Aromatase inhibitors in the breast cancer clinic: focus on exemestane

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Abstract

Breast cancer is the most prevalent type of cancer in women and responsible for significant female cancer-related mortality worldwide. In the Western world, over 80% of breast cancers are hormone-receptor positive for which endocrine therapy is administered. The main anti-estrogen treatments in use consist of selective estrogen-receptor modulators, such as tamoxifen, and third-generation aromatase inhibitors (AIs), such as exemestane, letrozole, and anastrozole. In this review, the focus will lie on exemestane, its clinical use, and its side-effect profile. Exemestane is the only third-generation steroidal AI. Its efficacy as a first-line treatment in metastatic breast cancer has been demonstrated. Therefore, exemestane could be considered a valid first-line therapeutic option, but it also can be used in second-line or further situations. Exemestane is mostly used as part of sequential adjuvant treatment following tamoxifen, but in this setting it is also active in monotherapy. Furthermore, this AI has been studied in the neoadjuvant setting as presurgical treatment, and even as chemoprevention in high-risk healthy postmenopausal women. It may reverse side effects of tamoxifen, such as endometrial changes and thromboembolic disease but may also cause some inconvenient side effects itself. Additionally, there is a lack of total cross-resistance between exemestane and nonsteroidal AIs as far as their anti-tumoral efficacy is concerned; moreover the two classes of AIs display a nontotal overlapping toxicity profile. Taking together, exemestane can be considered as a useful treatment option at all stages of breast cancer.

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Introduction

Breast cancer is the most common type of cancer in women and the main cause of female cancer-related deaths worldwide (Jemal *et al.* 2011). About 80% of primary breast cancers are hormone sensitive as they contain estrogen receptor (ER) and/or progesterone receptor-positive cells (Keen & Davidson 2003, Nadji *et al.* 2005). This type of breast cancer can be managed with endocrine therapy. The latter consists of either blocking the ER with an antagonist or reducing the endogenous production of estrogens.

Tamoxifen, a selective estrogen-receptor modulator (SERM), is one major type of endocrine treatment administered to women with hormone receptor (HR)-positive breast cancer. Adjuvant tamoxifen treatment can be administered for 5 years, whereby the rate of recurrence is lowered throughout the first decade, and breast cancer

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mortality is reduced by about a third throughout the first 15 years (Davies *et al*. 2011). The recent Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial has found that continuing tamoxifen treatment up to 10 years further reduced recurrence and mortality compared with stopping therapy at 5 years (Davies *et al*. 2013). This has now also been confirmed by data from the adjuvant Tamoxifen–To offer more? (aTTom) trial presented at the 2013 ASCO meeting (Gray *et al*. 2013).

Another important type of anti-estrogen therapy is treatment with aromatase inhibitors (AIs). This hormone therapy is typically administered in postmenopausal breast cancer patients as it is contra-indicated in women with residual ovarian function because it indirectly increases estrogen production which can induce mammary tumor proliferation (Smith & Dowsett 2003). AIs can be subdivided in two major groups: steroidal AIs (SAIs) and nonsteroidal AIs (NSAIs). Both groups of AIs block aromatase activity. Aromatase is a member of the cytochrome P450 (CYP) family enzymes, which converts androstenedione to estrone and testosterone to estradiol (E_2) (Dutta & Pant 2008). In this way, estrogen synthesis is inhibited.

According to the chronologic order of their clinical development, AIs are also classified as first-, second-, and third-generation inhibitors. Aminoglutethimide was a first-generation, fadrozole and rogletimide second-generation, and anastrozole and letrozole are third-generation NSAIs. In the SAI class, testolactone and formestane (4-hydroxyandrostenedione) are the first- and second-generation inhibitors respectively. Exemestane is the only representative of the third-generation steroidal inhibitors (Smith & Dowsett 2003).

Currently, the third-generation AIs such as, exemestane, letrozole, and anastrozole, are used in the treatment of HR-positive breast cancer. The focus of this report will be on exemestane, its clinical use, and its side effect profile, in line with the other AIs and tamoxifen.

Exemestane

Pharmacology

SAIs and NSAIs inhibit the enzyme aromatase in different ways (Lombardi 2002). SAIs such as exemestane are analogs of the natural aromatase substrate androstenedione. They bind covalently to the substrate-binding site of aromatase and hereby irreversibly inactivate the enzyme. NSAIs such as letrozole and anastrozole, on the other hand inhibit aromatase in a reversible manner by binding to the heme moiety of the enzyme. In this way, NSAIs prevent androgens from binding to the catalytic site. Clinical studies found 25 mg/day of exemestane, orally administered, to be the minimum effective dose producing maximum estrogen suppression (Evans *et al*. 1992, Johannessen *et al*. 1997, Paridaens *et al*. 1998). The mean maximum suppression of aromatase by exemestane is 97.9% (Geisler *et al*. 1998). For all third-generation AIs, 98% inhibition of total body aromatization has been reported whereas for first- and second-generation AIs only $<$90% has been achieved (Lønning & Eikesdal 2013).

An indirect comparison by Lønning & Geisler (2010) revealed that exemestane administered at 25 mg daily seemed to inhibit aromatization as efficiently as anastrozole administered at 1 mg daily. Furthermore 2.5 mg letrozole daily appeared to be a more potent inhibitor of aromatase compared with both alternatives (Geisler *et al*. 2002). Results, however, should be interpreted carefully considering plasma estrogen level measurements. To detect more than 90% inhibition *in vivo*, assays with a sensitivity limit of 5–7 pM for estrone and 1–2 pM for E_2 are required. Consequently, methods to evaluate such low-plasma estrogen levels in patients require a high sensitivity which makes measurement *in vivo* very difficult. Our research group developed a sensitive liquid chromatography–tandem mass spectrometry method for measuring low-estrogen levels (Pauwels *et al*. 2013). The limit of quantification is 1.2 and 1.3 ng/l for estrone and E_2 respectively. Exemestane, however, is metabolized into several steroidal compounds. These steroidal molecules may nonspecifically interact during the measurement of estrogen levels and consequently cause cross-contamination (Johannessen *et al*. 1997). As a result, chromatographic sample purification is required.

The question remains whether at very low levels of circulating estrogens, thus at more than 90% inhibition, there is a connection between anti-tumoral effect and hormonal suppression. Complicating this, however, are the potential roles of intratumoral aromatase activity/downregulation and drug metabolism in determining its efficacy for inhibiting tumor growth.

It is worth noting that breast cancer incidence in postmenopausal women is considered to be correlated with body fat. Adipose tissue physiologically expresses aromatase, but in obese women this expression is abnormally high. This leads to local overproduction of estrogens which stimulates tumor growth (Bulun *et al*. 2012). Consequently, obese patients may require higher AI dosages to achieve same efficacy, but results from previous

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studies seem to be inconsistent (Dixon *et al*. 2008, Goodwin & Pritchard 2010, Diorio *et al*. 2012).

Furthermore, estrogen levels, and particularly E_2, in breast tumor tissue are significantly higher than plasma estrogen levels (Vermeulen *et al*. 1986). These elevated intratumor levels may reflect the high concentration of ERs which allow increased binding of circulating estrogen, or enhanced intratumoral hormone synthesis (Lønning & Geisler 2010, Lønning *et al*. 2011). One study ascribed elevated tissue E_2 to a high concentration of ERs (Haynes *et al*. 2010). They, as well as other researchers, reported an increased E_2:estrone ratio compared with normal tissue due to increased expression of an oxidative isoform of 17β-hydroxysteroid dehydrogenase (Reed *et al*. 1989, Haynes *et al*. 2010). The source of intratumoral estrogen is still in debate and further studies are warranted.

A limited amount of studies compared clinical efficacy of SAIs and NSAIs in patients with hormone-dependent metastatic breast cancer. In one trial, 130 postmenopausal women with advanced breast cancer were randomized to receive anastrozole or exemestane for at least 8 weeks. Another trial randomized 103 postmenopausal women with advanced breast cancer to anastrozole or exemestane until they had disease progression. Both studies showed no difference in clinical efficacy between exemestane and anastrozole (Campos *et al*. 2009, Llombart-Cussac *et al*. 2012). Riemsma *et al*. (2010) indirectly compared different AIs in postmenopausal patients with HR-positive advanced or metastatic breast cancer. The authors reported a higher objective response rate (ORR) for letrozole and exemestane than for anastrozole, although no significant differences between AI treatment arms were identified with regard to overall survival (OS) and progression-free survival (PFS).

Clinical use

Metastatic breast cancer

At first diagnosis, ~6% of breast cancer patients present with metastatic disease. The remaining patients, diagnosed with apparently localized primary breast cancer, have a 20–50% chance of developing metastatic disease later, sometimes after more than two decades (Lu *et al*. 2009).

Treatment with endocrine therapy in metastatic breast cancer patients with HR-positive tumors is at least as efficacious as chemotherapy, if not more so (Glück 2009). Furthermore, it is generally better tolerated than chemotherapy. Exemestane, letrozole, and anastrozole have demonstrated clinical superiority when compared with conventional hormonal treatment, such as tamoxifen and first or second generation AIs (Smith & Dowsett 2003, Coombes *et al*. 2004, Lønning 2004, Howell *et al*. 2005, Jakesz *et al*. 2005, Thürlimann *et al*. 2005). In Table 1, all randomized trials are presented, in which third generation AIs were compared as first-line treatments with tamoxifen. Letrozole and anastrozole make up the treatment of choice in first-line therapy for metastatic disease (Winer *et al*. 2005). The Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability (TARGET) study and the North American trial compared first-line anastrozole treatment with tamoxifen therapy (Bonneterre *et al*. 2000, Nabholtz *et al*. 2000). In the TARGET trial, 668 postmenopausal women were randomized to receive either anastrozole or tamoxifen monotherapy. In the North American trial, 353 postmenopausal patients were recruited and randomized to anastrozole monotherapy or tamoxifen monotherapy. Both trials confirmed that anastrozole was valid as a first treatment choice instead of tamoxifen. In a randomized phase III study, letrozole was found to be significantly superior to tamoxifen as a first-line treatment (Mouridsen *et al*. 2003).

Although exemestane is often used as a second-line treatment (Glück *et al*. 2013), its efficacy as a first-line treatment was also demonstrated in the European Organisation for the Research and Treatment of Cancer (EORTC) trial (Paridaens *et al*. 2008). The EORTC Breast Cancer Cooperative Group undertook a phase III randomized open-label clinical trial to investigate the efficacy and tolerability of exemestane in comparison with tamoxifen in 371 postmenopausal patients with hormone-dependent metastatic breast cancer. Overall response rate was greater for the exemestane treatment arm compared with the tamoxifen treatment arm whereas no significant difference in OS was detected between treatment arms. OS was not significantly different from that for tamoxifen in the different individual trials of the three third-generation AIs, but a meta-analysis showed an OS benefit of using AIs compared with tamoxifen as first-line therapy for HR-positive breast cancer (Mauri *et al*. 2006). AIs can thus be considered more efficacious than tamoxifen in first-line therapy, which is of prime importance for quality of life in a noncurable palliative setting. AIs are also superior to megestrol acetate, a progestin. Previously, megestrol acetate was used as a standard second-line hormonal therapy in patients with breast cancer resistant to tamoxifen, but according to a phase III trial, overall ORRs were higher with exemestane vs megestrol acetate as second-line treatment following tamoxifen failure (Kaufmann *et al*. 2000, Walker *et al*. 2013).

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Table 1 Phase III clinical trials evaluating first-line aromatase inhibitors vs tamoxifen in advanced/metastatic breast cancer

Study (follow-up)[a]	Patients (n)[b]	Treatment	Median TTP/PFS (*P* value)	TTP/PFS risk (95% CI)	ORR (%, *P* value)	CBR (%, *P* value)	OS (*P* value)
EORTC-BCCG[c] 29 months	E, 182 T, 189	E vs T	9.9 vs 5.8 months (0.121)	0.84 (0.67–1.08)	46 vs 31 (0.005)	NR	1 year, 82 vs 86% (0.821)
TARGET study[d] 19 months	T, 328 A, 340	T vs A	8.3 vs 8.2 months (0.941)	0.99 (NR)	32.6 vs 32.9 (NR)	55.5 vs 56.2 (NR)	NR
The North American trial[e] 17.7 months	T, 182 A, 171	T vs A	5.6 vs 11.1 months (0.005)	1.44 (NR)	17.0 vs 21.1 (NR)	46 vs 59 (0.0098)	NR
Phase III study[f] 32 months	L, 453 T, 454	L vs T	9.4 vs 6.0 months (<0.0001)	0.72 (NR)	32 vs 21 (0.0002)	50 vs 38 (0.0004)	34 vs 30 months (NS)

A, anastrozole; CBR, clinical benefit rate (CR+PR+SD for ≥6 months); E, exemestane; EORTC-BCCG, European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group; HR, hazard ratio; L, letrozole; NR, not reported; NS, not significant; ORR, objective response rate (CR+PR); OS, overall survival; PFS, progression-free survival; T, tamoxifen; TARGET, Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability; TTP, time to progression.
[a]Median follow-up.
[b]Patients analyzed.
[c]Paridaens *et al*. (2008).
[d]Bonneterre *et al*. (2000).
[e]Nabholtz *et al*. (2000).
[f]Mouridsen *et al*. (2003).

In the Evaluation of Faslodex vs Exemestane Clinical Trial (EFECT), the time to progression for exemestane and fulvestrant (Faslodex), a complete ER antagonist, was demonstrated to be similar as well as the adverse event profile in a setting where tumors were refractory to a NSAI (Chia *et al*. 2008). It is noteworthy that in the EFECT trial, the conventional dose of fulvestrant (250 mg) was administered. Later in another trial it was found that with the present advised dose (500 mg), fulvestrant is at least as efficacious as exemestane as a second-line treatment in postmenopausal women with advanced breast cancer (Cope *et al*. 2013).

As a result of the order in which they were developed, third-generation NSAIs instead of SAIs are more often used as first-line treatment in metastatic disease. Upon progression of metastatic disease following treatment with NSAIs, exemestane may be effective as sequential hormone therapy (Lønning *et al*. 2000, Bertelli & Paridaens 2006, Steele *et al*. 2006, Lønning 2009, Lønning & Geisler 2010, Kim *et al*. 2012). Several trials have found that breast cancer patients who have become resistant to NSAIs may experience benefit from SAIs (Table 2; Thürlimann *et al*. 1997, Lønning *et al*. 2000, Bertelli *et al*. 2005, Iaffaioli *et al*. 2005, Gennatas *et al*. 2006, Mayordomo *et al*. 2006, Steele *et al*. 2006, Carlini *et al*. 2007, Chin *et al*. 2007, Mauriac *et al*. 2009). On average, 25–30% of patients in these cross-over studies experienced objective response or stable disease for 6 months or more. Conversely, administration of NSAIs seems to be effective after failing SAIs as well (Table 2; Bertelli *et al*. 2005, Mayordomo *et al*. 2006). Several potential mechanisms underlying this nontotal cross-resistance have been suggested, but studies exploring which mechanisms are actually responsible are eagerly awaited.

Taking all these data into account, one can conclude that exemestane as first-line treatment is effective, well tolerated, and can be considered, like NSAIs, as a valid first-line option for treatment of HR-positive cancers in postmenopausal women (Glück 2009). As far as hormonal suppression is concerned, exemestane seems slightly less efficacious when compared with the other AIs, whereas the clinical anti-tumoral efficacy of NSAIs and SAIs seems to be similar. In second-line treatment, the sequence of AIs does not seem to matter as a result of nontotal cross-resistance.

Adjuvant setting

Upfront treatment As stated above, 5 years of treatment with tamoxifen remained for more than two decennia the standard adjuvant anti-hormonal treatment for postmenopausal patients. The first trials aiming at integrating AIs into the adjuvant setting explored various schedules, compared with 5 years tamoxifen which was considered to be the standard reference treatment.

The first schedule was 5 years treatment with AIs instead of 5 years of tamoxifen, in which mainly NSAIs were studied. The Arimidex, Tamoxifen Alone or in Combination (ATAC) trial compared the safety and

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Table 2 Cross-over clinical trials in advanced/metastatic breast cancer

Patients (*n*)[a]	First AI	Second AI	TTP	ORR (%)	CBR (%)	References
78	AG	E	21 weeks	26	39	Thürlimann *et al.* (1997)
241	AG, A, L, V	E	14.7 weeks	6.6	24.3	Lønning *et al.* (2000)
18	E	L (A)	9.3 months	22.2	55.6	Bertelli *et al.* (2005)
23	A, L	E	5.1 months	8.7	43.5	Bertelli *et al.* (2005)
50	A	E	5 months	8	44	Iaffaioli *et al.* (2005)
60	A, L	E	3.2 weeks	20.0	38.3	Gennatas *et al.* (2006)
12	A	E	4.4 months	NR	NR	Mayordomo *et al.* (2006)
11	E	A	1.9 months	NR	NR	Mayordomo *et al.* (2006)
108	A, L	E	18 months	5	46	Steele *et al.* (2006)
30	A, L	E	4 months	NR	46.6	Carlini *et al.* (2007)
31	A, L	E	3.2 months	19.4	54.8	Chin *et al.* (2007)
184[b]	A, L	E	2.8 months	4.4	27.2	Mauriac *et al.* (2009)
239	A, L	E	4.1 months	0.4	64.8	Baselga *et al.* (2012)

A, anastrozole; AG, aminoglutethimide; CBR, clinical benefit rate (CR + PR + SD for ≥6 months); E, exemestane; L, letrozole; NR, not reported; ORR, objective response rate (CR + PR); TTP, time to progression; V, vorozole.
[a]Patients analyzed.
[b]Patients with visceral metastases.

efficacy of tamoxifen monotherapy, anastrozole monotherapy, and tamoxifen–anastrozole combination therapy for 5 years (Baum *et al.* 2002). We learned from this trial that tamoxifen should not be combined with AIs and that NSAIs were slightly but significantly superior to tamoxifen.

Further, switch strategies were explored for all three AIs in which 2–3 years of tamoxifen are followed by 2–3 years of AI therapy. The Intergroup Exemestane Study (IES) conducted a trial to compare 5 years tamoxifen with a sequential therapy consisting of a sequence of tamoxifen followed by exemestane (called the exemestane 'switch') for a total of 5 years in postmenopausal patients with early, HR-positive breast cancer (Coombes *et al.* 2004). After 2–3 years of tamoxifen treatment, patients were randomized in an intent-to-treat analysis to receive either tamoxifen or exemestane. A significantly higher disease-free survival (DFS) was reported in the exemestane treatment arm. Based on these results, the exemestane 'switch' was considered a valuable adjuvant option. Later on, the Tamoxifen Exemestane Adjuvant Multinational (TEAM) phase III trial investigated the potential of 5 years exemestane as an alternative to 5 years tamoxifen. The trial had to be modified because the results of the IES were published while the TEAM trial was still ongoing, indicating that 5 years adjuvant tamoxifen might be considered as a suboptimal adjuvant treatment. The modified TEAM design compared long-term effects of exemestane monotherapy for 5 years with the tamoxifen/exemestane 'switch' strategy in postmenopausal women with HR-positive breast cancer (van de Velde *et al.* 2011). Results showed no significant differences in DFS and OS between both groups.

The Breast International Group (BIG) 1–98 trial was conducted to ascertain the efficacy of the switch strategy vs 5 years of AI therapy (Regan *et al.* 2011). The BIG 1–98 trial was a four-arm trial wherein 5 years of letrozole or tamoxifen monotherapy or sequences of 2 years of one followed by 3 years of the other were compared with each other. The authors found that efficacy with sequential therapy was not significantly different from that with letrozole monotherapy, while tamoxifen only was inferior to the three arms including an AI. The investigators, however, found that DFS and OS in the sequential treatment arm were, although nonsignificant, inferior in comparison with monotherapy at a median follow-up of 71 months. The results concerning DFS and OS between 'switch' strategy and monotherapy contrast with what was observed in the TEAM trial. Thus, so far, it is not yet known whether AI monotherapy or sequential therapy should be preferred.

Taken together, AI treatment should be preferred as standard adjuvant endocrine therapy, but the question remains which AI should be given preference as first-line therapy. This was addressed in the MA.27 trial which compared exemestane with anastrozole as a 5 years initial adjuvant treatment in postmenopausal women (Goss *et al.* 2013). The authors reported similar efficacy for both treatment options and thus suggested exemestane also as a safe and effective option as first-line adjuvant treatment in postmenopausal women with HR-positive breast cancer.

Based on the above results, AIs have become a standard adjuvant endocrine therapy for postmenopausal

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breast cancer patients and have proven superiority to tamoxifen monotherapy (Coombes *et al*. 2004, van de Velde *et al*. 2010, Rao & Cobleigh 2012, Boccardo *et al*. 2013).

Extended treatment Studies have shown that an endocrine therapy schedule of 5 years is more efficacious than one of 2 or 3 years (Abram *et al*. 1996, Swedish Breast Cancer Cooperative Group 1996). The question remains, however, whether extending therapy with an additional 5 years of adjuvant treatment is more efficacious in comparison with the standard 5 years anti-estrogen therapy.

As stated earlier, the ATLAS and the aTTom trials demonstrated that extending therapy to 10 years of tamoxifen instead of 5 years for patients with HR-positive breast cancer further reduces recurrence and mortality (Davies *et al*. 2013, Gray *et al*. 2013).

There are studies which investigated the effects of prolonging 5 years tamoxifen treatment with 5 years of treatment with an AI. The National Surgical Adjuvant Breast and Bowel Project B-33 trial (NASBP-B33) randomly assigned postmenopausal breast cancer patients who were disease-free after 5 years of tamoxifen treatment to one of two treatment arms comprising either 5 years of exemestane treatment or 5 years of placebo treatment (Mamounas *et al*. 2008). This study showed a nonsignificant improvement in DFS for the exemestane group. A significant improvement in relapse-free survival was seen at a median follow-up of 30 months. Letrozole following 5 years of tamoxifen treatment also improves DFS and distant-free survival in patients with HR-positive breast cancer according to the MA.17 trial (Goss *et al*. 2005). Extended letrozole treatment is well-tolerated. The Study of Letrozole Extension (SOLE) in postmenopausal women with breast cancer is a currently ongoing randomized trial wherein extended continuous letrozole treatment is compared with intermittent letrozole treatment following 4–6 years of prior adjuvant endocrine therapy (Colleoni 2011). The Adjuvant post-Tamoxifen Exemestane vs Nothing Applied (ATENA) trial was an open-label trial in which postmenopausal patients were randomized to 5 years of exemestane treatment or 5 years of observation after 5–7 years of tamoxifen administration (Markopoulos *et al*. 2009*a*). This trial, however, was prematurely ended because results of the MA.17 trial were published. Furthermore, to date, no trials have, to our knowledge, investigated the efficacy of 10 years of AI treatment instead of 5 years.

Neoadjuvant setting

Neoadjuvant therapy makes conservative surgery possible in a high percentage of breast cancer patients and its use is increasing. Chemotherapy is mostly applied in this setting, although AIs may also play an important role. In a randomized phase II trial, the effects of presurgical treatment with letrozole, anastrozole, or exemestane in postmenopausal women with ER-rich stage 2 or 3 breast cancer were investigated (Ellis *et al*. 2011). Results showed improved surgical outcomes in patients treated with neoadjuvant AI therapy and that these AIs are biologically equivalent.

In a phase II study investigating presurgical treatment with exemestane for 6 months in postmenopausal patients with ER-positive breast cancer, a beneficial effect of this therapy was observed (Barnadas *et al*. 2009). Treatment for conservative surgery appeared to be effective and well tolerated.

Another randomized phase II trial, PTEX46, investigated the optimal duration of neoadjuvant exemestane treatment (Hojo *et al*. 2013). Fifty-one postmenopausal women with HR-positive invasive breast cancer were randomized to neoadjuvant exemestane treatment for 4 or 6 months. No difference in the outcome of breast-conserving surgery was observed between the different treatment-duration groups. Thus, a 4-months treatment with exemestane appears to be warranted in postmenopausal patients awaiting breast-conserving surgery. Based on these results, exemestane should be considered a valid option in the neoadjuvant setting.

Breast cancer-off label use

Premenopause

AIs are mainly used as adjuvant treatment for early HR-positive breast cancer in postmenopausal patients (Nordman *et al*. 2005). In premenopausal patients, standard of care in the adjuvant setting is 5–10 years treatment with tamoxifen (Rao & Cobleigh 2012). Tamoxifen combined with ovarian function suppression or ablation is deemed superior to first-line tamoxifen monotherapy in the case of metastatic disease (Paridaens *et al*. 2010). Aromatase inhibition is not recommended in premenopausal women, because inhibition of the hypothalamus pituitary aromatase induces an increase in gonadotropins which in turn stimulate ovarian follicular growth, producing high levels of circulating estrogen which can thereby induce mammary tumor proliferation (Simpson 2003). As proof of this, let us remember that AIs

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in young women are also used for the stimulation of ovaries, as treatment of infertility (Polyzos *et al*. 2009). For these reasons, AIs are formally contra-indicated in women with residual ovarian function. They can, however, safely be given in combination with reversible or irreversible ovarian ablation.

In 1803 premenopausal women with early breast cancer, the Austrian Breast and Colorectal Cancer Study (ABCSG-12) tested the addition of AIs to ovarian suppression achieved by goserelin, a gonadotropin-releasing hormone (GNRH) agonist (Gnant *et al*. 2009). All patients received goserelin and were randomly assigned to either tamoxifen or anastrozole for 5 years, with or without zoledronic acid for 3 years. DFS was similar in all groups, but OS was inferior in the anastrozole monotherapy group (Gnant *et al*. 2011).

Currently, two ongoing trials are investigating adjuvant exemestane in premenopausal women combined with suppression of their ovarian function. In the Suppression of Ovarian Function Trial (SOFT), 5 years tamoxifen treatment – the reference for premenopausal patients – is compared with tamoxifen plus ovarian function suppression or exemestane plus ovarian function suppression. The latter is accomplished by administering 5 years of treatment with the GNRH analog triptorelin, surgical oophorectomy, or ovarian irradiation (Zickl *et al*. 2012). The Tamoxifen and Exemestane Trial (TEXT) compares 5-year treatment with triptorelin plus tamoxifen with 5 years triptorelin plus exemestane (Zickl *et al*. 2012). Results from both studies, which have completed their accrual, are eagerly awaited.

In some premenopausal women with chemotherapy-induced amenorrhea, however, recovery of ovarian function occurs when these patients are treated with AIs (Smith *et al*. 2006, Ortmann *et al*. 2009). Ten percent of patients experienced resumed bleeding within the subsequent 3 years (Sukumvanich *et al*. 2010). Chemotherapy-induced amenorrhea in premenopausal breast cancer patients is thus not always irreversible, and hormonal assays are not predictive in this regard, so that one should be careful when administering adjuvant AIs in younger women. The question remains, from what age adjuvant treatment with an AI should be considered safe. In practice, tamoxifen could first be given for several years, allowing an AI switch later, eventually to be delayed beyond the age of 50 years. In addition, the practical guideline produced by De Vos *et al*. (2012) could be used to establish a patient's menopausal status.

In summary, AIs are contra-indicated in premenopausal breast cancer patients with hormonally active gonads. Preliminary results of the randomized ABCSG-12 trial comparing GNRH analogs with either tamoxifen or anastrazole show no significant difference in relapse rates, but many more events are necessary to make powerful comparisons. Likewise, the results of the SOFT and the TEXT study are eagerly awaited.

Aromatase inhibition in men

In Europe, 1 out of 100 000 men/year will develop breast cancer (Fentiman *et al*. 2006), which represents 1% of all breast cancer patients. A family history of breast cancer, exogenous estrogens, and therapeutic or diagnostic radiation are the risk factors for men to develop breast cancer (Fentiman *et al*. 2006).

The treatment options include surgery, adjuvant loco-regional radiotherapy, and/or systemic therapy (Fentiman *et al*. 2006). Up to 90% of male breast cancers are HR-positive (Rayson *et al*. 1998) and therefore, adjuvant endocrine therapy or combined endocrine and chemotherapy are mainly administered (Agrawal *et al*. 2007). Herein tamoxifen is the standard of care. AIs, however, are suggested to have survival benefit compared with tamoxifen in female postmenopausal breast cancer patients with metastatic HR-positive breast cancer. In contrast, OS in men was significantly increased with tamoxifen compared with AIs (Eggemann *et al*. 2013). This could be explained by the 'feedback loop' hypothesis. Testicular production of estrogen in men accounts for ~20% of circulating estrogens and this part is independent of aromatase; the remaining 80% of circulating estrogen in men is formed by peripheral aromatization of androgens (Agrawal *et al*. 2007). Chronic administration of AIs causes a significant decrease in plasma E_2, but testicular production of estrogen is not inhibited. Therefore, estrogen levels are suboptimally decreased and there is less suppression in men compared with women. Furthermore, testosterone and follicle-stimulating hormone are increased with long-term AI treatment. Taken together, the changes in hormone levels via this feedback loop could lead to an increase in substrate for aromatization (Giordano & Hortobagyi 2006, Doyen *et al*. 2010).

Additionally, increased testosterone levels caused by exemestane treatment seem to stimulate tumor growth in men with prostate carcinoma (Bonomo *et al*. 2003). As a result, tamoxifen should be considered the treatment of choice for men with HR-positive breast cancer in the adjuvant setting. For treating metastatic disease, AIs may be helpful, but should be only administered in

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combination with agents blocking the testicular production of steroid hormones, e.g. GNRH analogs (Zagouri *et al*. 2013).

Side effects

Many women undergoing natural menopause experience inconveniences caused by a decrease in estrogen levels (Shanafelt *et al*. 2002). These side effects may be particularly pronounced in young women when menopause is abruptly induced by chemotherapy or ovarian ablation. Similar troubles arise in breast cancer patients treated with AIs due to further estrogen synthesis suppression. Therefore, several AI-induced side effects such as hot flashes, musculoskeletal symptoms, cardiovascular events, and sexual dysfunction are believed to be associated with the AI-induced estrogen deficiency (Ahlborg *et al*. 2003).

Hot flashes

Hot flashes are one of the most common side effects reported under tamoxifen and AI therapies (Kittaneh & Glück 2011), with a frequency up to 50% (Shanafelt *et al*. 2002).

Both randomized adjuvant IES and TEAM trials reported high numbers of hot flashes among postmenopausal breast cancer patients treated with exemestane (Coombes *et al*. 2004, 2007, van de Velde *et al*. 2011). In a TEAM substudy, hot flashes complaints were compared between the first year of either adjuvant exemestane or tamoxifen treatment (Jones *et al*. 2007). The mean hot flash score of both groups peaked at 3 months of therapy, and subsequently decreased. After 12 months, a lower hot flash frequency was found with exemestane then with tamoxifen.

One prospective, cross-over study scored hot flashes after switching to letrozole or exemestane in postmenopausal women who already experienced hot flashes on adjuvant tamoxifen (Thomas *et al*. 2008). The authors found a significant improvement following treatment with AIs. The intensity of hot flashes was slightly lower if patients were treated with exemestane compared with letrozole.

The NCIC CTG MA.27 randomized controlled phase III trial evaluated vasomotor symptoms of anastrozole-treated and exemestane-treated patients (Goss *et al*. 2013). No significant differences were seen between the two treatment groups. Taking these data together, it can be concluded that fewer hot flashes occur for treatment with AIs compared with treatment with tamoxifen. To reduce symptomatic hot flashes and if conventional lifestyle measures fail, nonhormonal treatments, e.g. clonidine, venlafaxine, or gabapentine are generally administered (Shanafelt *et al*. 2002). In contrast to concomitant tamoxifen use, SSRIs are generally not contra-indicated during AI treatment.

Bone metabolism

Owing to its estrogen-like effect on bone, tamoxifen inhibits bone resorption in postmenopausal women thereby exerting a protective effect against osteoporosis. On the other hand, as a consequence of the estrogen-lowering effect of AIs, rate of bone turnover, loss of bone mineral density (BMD), and the incidence of fractures increase in postmenopausal breast cancer patients treated with these agents, as suggested in the ATAC trial, BIG 1–98 study and the IES (Coleman *et al*. 2010, Eastell *et al*. 2011, Zaman *et al*. 2012).

Anastrozole accelerates bone loss as a result of increased bone turnover leading to reduced BMD (Eastell *et al*. 2008). Similarly, exemestane causes an increase in bone turnover markers and reduces BMD (Lønning *et al*. 2005). The same decrease was recorded when patients were treated with letrozole (Perez *et al*. 2006) or after completing 5 years of adjuvant tamoxifen therapy (Gonnelli *et al*. 2007). For the latter study, bone loss could be explained firstly by the estrogen-reducing effect of exemestane and secondly by the loss of the protective effect of tamoxifen as well. This is attested by a significant increase in bone turnover markers already detected after 6 months tamoxifen withdrawal and exemestane initiation. Bone turnover markers were significantly increased at 6 months with respect to tamoxifen withdrawal and exemestane initiation.

The annual fracture incidences in women treated with anastrozole or letrozole were 21.6 and 22.0/1000 women-years, respectively, according to the ATAC and BIG 1–98 trials. Under exemestane, this was 19.2/1000 women-years (Coleman *et al*. 2007). Reassuringly, increased bone loss was found to be reversed after discontinuing the anti-aromatase treatment (Coleman *et al*. 2010).

To prevent and treat AI-induced bone loss, patients typically receive calcium and vitamin D supplements. BMD should also be monitored every 2 years as long as AI treatment is continued. Additionally, bisphosphonate therapy or treatment with receptor activator for nuclear factor-κB ligand (RANKL) inhibitors, such as denosumab, could be administered to patients at increased risk of fractures or osteoporosis, smokers and patients taking oral

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corticosteroids for more than 6 months (Gnant *et al*. 2007, Eastell *et al*. 2008, Hadji *et al*. 2008, Gaillard & Stearns 2011). In conclusion, exemestane, like other AIs, is associated with increased bone turnover, loss of BMD, and an increased incidence of fractures, thus requiring close observation and, if needed, treatment.

Musculoskeletal symptoms

Although the reported incidences of AI-induced musculoskeletal symptoms range from 5–36.0% in the large clinical trials (Howell *et al*. 2005, Coombes *et al*. 2007, Crew *et al*. 2007, Gaillard & Stearns 2011), more than half of patients complain of these adverse events in the clinical setting (Presant *et al*. 2007, Lintermans & Neven 2011). The lowest incidence has been reported for exemestane-treated patients in the IES. However, other reports did not show differences in incidences of musculoskeletal symptoms between the three AIs (Crew *et al*. 2007). These conflicting results are due to the variable definitions used in the several trials.

Musculoskeletal symptoms often lead to a decreased quality of life and, consequently, compromise adherence and lead to therapy discontinuation. The most encountered symptoms include new or worsened carpal tunnel syndrome; trigger finger; morning stiffness; and pain of wrists, hands, knees, hips, back, ankles, feet, and shoulders (Henry *et al*. 2008, Mao *et al*. 2009, Gaillard & Stearns 2011). A retrospective evaluation of the IES showed higher rates of carpal tunnel syndrome in patients treated with exemestane when compared with those treated with tamoxifen (Mieog *et al*. 2012). In most patients, symptoms occur rapidly, generally, within the first 3 months of AI therapy (Henry *et al*. 2008, Mao *et al*. 2009), though delayed onset can also occur in some patients.

There is a growing interest in defining proper biomarkers in order to identify patients at risk of developing these bothers. Reported clinical risk factors include prior taxane-based chemotherapy, time since menopause, low BMI, and baseline arthralgia (Crew *et al*. 2007, Mao *et al*. 2009).

Underlying mechanisms still remain not fully understood. Our group and others demonstrated tenosynovial changes and intra-articular fluid accumulation, on magnetic resonance imaging and ultrasonography in patients who reported severe AI-induced musculoskeletal pain (Morales *et al*. 2007, Henry *et al*. 2010, Lintermans *et al*. 2011, 2013). The etiology is still largely unknown and improvement of symptoms is rarely seen after administration of nonsteroidal anti-inflammatory drugs, the most commonly used strategy to tackle these problems. As a consequence, up to one out of four patients may discontinue treatment (Lintermans & Neven 2011).

Another emerging hypothesis proposes a role for vitamin D. Indeed vitamin D deficiency is common in postmenopausal breast cancer patients and is associated with worse outcome (Hatse *et al*. 2012). Consequently, recent studies have reported that daily vitamin D supplements may have a protective effect on pathogenesis (Khan *et al*. 2010, Rastelli *et al*. 2011). This observation may represent a promising possibility for maintaining quality of life and for preventing discontinuation of a potentially life-saving adjuvant anticancer treatment.

Lipid metabolism

Natural or induced menopause, with low levels of circulating estrogens, frequently leads to increased levels of LDL cholesterol and decreased HDL cholesterol levels. These changes are considered to increase the risk of the development of coronary heart disease (Gorodeski 2002). Tamoxifen has a favorable effect on lipids (mainly by decreasing levels of LDL, the atherogenic fraction of cholesterol), whereas AIs may have a further negative effect on these lipid parameters.

In contrast with tamoxifen, NSAIs do not have a protective effect on lipid metabolism. Most studies, however, did not show marked changes in lipid parameters induced by letrozole or anastrozole (Nabholtz 2008). In addition, no detrimental effect on atherogenic indices was seen for exemestane. Exemestane has no effect on levels of total cholesterol or its fractions, nor on lipoprotein levels (Atalay *et al*. 2004). A TEAM substudy compared the effect of exemestane on lipid metabolism to that of tamoxifen (Markopoulos *et al*. 2005). For triglyceride levels, no significant mean difference across time was seen between tamoxifen and exemestane (Markopoulos *et al*. 2009*a*). Another randomized study in early breast cancer patients showed no major effect of exemestane on serum lipids compared with placebo (Lønning *et al*. 2005). Both treatments decreased total cholesterol levels. The ATENA trial evaluated the effect of extending adjuvant therapy with exemestane for 2 years after completion of 5 years of tamoxifen treatment. This extended regimen did not induce significant effects on lipid profiles during the 24 months of the study (Markopoulos *et al*. 2009*b*). Consequently, data from both trials were reassuring.

As can be concluded from these studies, exemestane seems to have an almost neutral effect on lipids. Whether

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it will translate into an increased risk of cardiovascular disease remains to be shown by long-term follow-up data in adjuvant trials, as is also the case for NSAIs.

Cardiovascular adverse events

With advancing age, the heart undergoes subtle physiological changes and subsequently cardiovascular diseases such as hypertension, coronary heart disease, heart valve disease, and rhythm disorders, become increasingly common (Young *et al*. 2000). Consequently, among postmenopausal women, cardiovascular diseases occur more frequently (Ewer & Glück 2009).

Owing to its cholesterol-lowering effect, tamoxifen therapy has beneficial effects on the cardiovascular system. However, it is well-known that tamoxifen increases the risk of thromboembolic events (Meier & Jick 1998), as was demonstrated by the higher frequency of thromboembolic disease in patients who received tamoxifen in the IES-control arm compared with exemestane users (Coombes *et al*. 2004, 2007). Hypertension was increased in the latter group, which may explain why the overall incidence of cardiovascular events was similar in the two groups. Similar findings were reported in the TEAM trial (van de Velde *et al*. 2011).

In the MA.27 trial, myocardial infarction, stroke, and transient ischemic attacks were compared between patients receiving anastrozole or exemestane (Goss *et al*. 2013). For these events, no difference was observed between both treatment groups. However, atrial fibrillation was more frequently reported among exemestane users.

In summary, mild increases in cardiovascular risk have been observed with AI treatment compared with tamoxifen. This may reflect the fact that AIs do not display the well-known protective effect of tamoxifen, although no evidence is present of any increase as compared with placebo (Jakesz *et al*. 2005, Kaufmann *et al*. 2007, Forbes *et al*. 2008, Colleoni *et al*. 2011, Bliss *et al*. 2012, Dubsky *et al*. 2012, Boccardo *et al*. 2013).

Vaginal side effects

A TEAM substudy compared menopausal symptoms during the first year of adjuvant exemestane treatment vs tamoxifen treatment (Jones *et al*. 2007). No significant difference in vaginal bleeding was detected, but exemestane patients reported more vaginal dryness whereas tamoxifen users had significantly more vaginal discharge. The latter has also been reported in an IES substudy (Fallowfield *et al*. 2006); however, a difference in vaginal dryness could not be corroborated.

An increased vaginal dryness incidence was similarly reported for anastrozole in the ATAC substudy (Fallowfield *et al*. 2006). Letrozole therapy, when compared with placebo, showed no significant difference in vaginal dryness, as observed in the MA.17 trial (Goss *et al*. 2005). AI treatment has also been associated with a higher incidence of dyspareunia compared with individuals not treated with AIs (Wiggins & Dizon 2008, Mortimer 2010).

Cognition

ERs have been found in many parts of the brain involved in cognition suggest a role for estrogen in cognitive function (Gasbarri *et al*. 2011, Phillips *et al*. 2011*a*). Some reports indicate that estrogen supplementation has a beneficial effect on cognitive function, although results are still conflicting (Sherwin 2012). Accordingly, adjuvant endocrine therapy in postmenopausal breast cancer may influence cognitive function. Tamoxifen was negatively associated with cognitive functions in some reports (Paganini-Hill & Clark 2000, Collins *et al*. 2009) and the TEAM trial confirmed these findings by showing that tamoxifen is significantly associated with lower functioning in verbal memory and executive functioning (Schilder *et al*. 2010). Exemestane, on the other hand, did not show significantly worse outcomes for any cognitive domain compared with healthy controls.

The BIG 1–98 trial, comparing tamoxifen to letrozole, indicated that, during the fifth year of treatment, the cognitive function of the letrozole-treated group was better than that of the tamoxifen-treated group. It is noteworthy that cognitive function improved consistently after cessation of treatment (Phillips *et al*. 2011*b*).

The International Breast Intervention Study II (IBIS II) found no significant difference between the anastrozole-treated and placebo groups in high-risk women (Jenkins *et al*. 2008). In contrast, one pilot study of the ATAC trial showed that both anastrozole-treated and tamoxifen-treated patients had decreased verbal memory and processing speed compared with patients that had received placebo (Jenkins *et al*. 2004). Consequently, results about the effect of AIs on cognition are still conflicting; they seem anyhow less pronounced than the effects of tamoxifen but more studies are warranted to ascertain this.

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Perspectives

Predicting response

About 30% of breast cancer patients receiving endocrine treatment relapse or become resistant to their therapy (Beelen *et al.* 2012). Therefore, biomarkers capable of predicting resistance are of major clinical interest. Tumor cell characteristics like nuclear receptor status, ERα modifications, variation in cofactor expression, and cell cycle regulation may be very relevant parameters. Also, activated growth-factor pathways such as phosphoinositide 3 kinase (PI3K), epidermal growth factor receptor 1 (HER1) and HER2, and estrogen and drug metabolism could be involved in the development of resistance as well (Beelen *et al.* 2012). The development of resistance to anti-estrogen treatment in breast cancer has been linked to activation of the PI3K–Akt–mTOR signaling pathway. Inhibition of proliferation could then be synergistically enhanced by the addition of a mTOR inhibitor to the endocrine treatment (Boulay *et al.* 2005). The Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study investigated the safety and efficacy of adding the mTOR inhibitor, everolimus, to exemestane therapy in breast cancer patients who had been previously treated with NSAIs (Baselga *et al.* 2012). The study showed that concomitant use prolonged PFS. Nonetheless, combination therapy was associated with a higher incidence of adverse events when compared with exemestane monotherapy as well as a higher percentage of treatment discontinuation (Dhillon 2013). Despite its prolonged PFS, cost-effectiveness of this combination therapy is still under debate due to the amount of side effects of mTOR inhibitors (Peterson 2013).

The BALLET study is a similar study which is currently ongoing. In this trial everolimus–exemestane combination therapy is administered to postmenopausal women with ER-positive locally advanced or metastatic breast cancer resistant to NSAIs. The primary objective is to evaluate the safety of everolimus treatment. As the study is ongoing, no data are available yet. Furthermore, efficacy of letrozole plus the mTOR inhibitor, temsirolimus, was investigated in another randomized phase III trial (Wolff *et al.* 2013). In this study, the combination was administered as a first-line treatment to postmenopausal women with AI-naïve locally advanced or metastatic breast cancer. Results showed that letrozole plus temsirolimus did not improve PFS. These findings are in contrast to the findings from the BOLERO2 trial. The lack of complete cross-resistance between the different AI classes was confirmed in these phase III trials as SAIs were administered to patients who experienced recurrence after treatment with NSAIs and this resulted in a prolonged PFS.

It has been found that changing from one AI-class to another, regardless of the sequence, can result in 0–26% ORR and that 50–62% of these patients achieve stable disease (Thürlimann *et al.* 1997, Zilembo *et al.* 2004, Bertelli *et al.* 2005, Chia *et al.* 2008, Miller *et al.* 2008). The exact mechanism of nontotal cross-resistance however is not yet known. One explanation could be the variance in AIs which results in different sensitivity. Polymorphisms in the aromatase gene such as single nucleotide polymorphisms (SNPs) could predict response of AIs in breast cancer. For instance, two tightly linked SNPs in CYP19 were significantly associated with improved efficacy of letrozole (Wang *et al.* 2010). In contrast, a polymorphism at the 3′-UTR region of the aromatase gene defines a subgroup of patients refractory to neoadjuvant letrozole associated with poor prognosis (Garcia-Casado *et al.* 2010). Another possible explanation is the *in vivo* androgen agonistic effects of 17-hydro-exemestane, a metabolite of exemestane. Most breast tumors contain more than 10 fmol/mg protein androgen receptors (Lea *et al.* 1989). When estrogen levels are reduced, breast cancer cells are more sensitive to the protecting effect of androgens and consequently their proliferation can be inhibited by androgens or androgen agonists (Macedo *et al.* 2006, Suzuki *et al.* 2007). This anti-tumor effect might also occur with AIs because of their estrogen-suppressive effect, and as a result, this sensitizes tumor cells to androgen growth inhibition. However, further investigations remain necessary to clarify this topic, because the exact reason for lack of complete cross-resistance is still unknown and could be explained by the different mechanisms of action.

Currently, the influence on therapy efficacy is being investigated after the addition of several other signal transduction inhibitors such as inhibitors of the Ras–Raf-MEK–MAPK pathway, insulin-like growth factor 1 receptor, gamma secretase/Notch, cyclin-dependent kinase 4/6 (CDK4/6), histone deacetylase, and Src/Abl a.o., to AI treatment (Fedele *et al.* 2012).

In addition, biomarkers able to accurately discriminate responders and nonresponders to endocrine therapy are warranted, as they would play a major role in personalized medicine.

Chemoprevention

The three major options for reducing breast cancer occurrence in high-risk women are screening,

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chemoprevention, and prophylactic surgery. SERMs are considered a preventive treatment for breast cancer. Prophylactic use of tamoxifen reduces the risk of breast cancer development in women at high-risk by about 50% (Cuzick *et al*. 2002, Waters *et al*. 2010). In the adjuvant setting, 5 years of tamoxifen reduces recurrence, contralateral disease, and mortality by 30–50%. Additionally, AIs could be used as chemoprevention. The Mammary Prevention 3 (MAP.3) trial was implemented based on the fact that AIs have been shown to be more effective than tamoxifen at reducing contralateral breast cancer incidence as adjuvant therapy (Coombes *et al*. 2007, Goss *et al*. 2011, Dunn *et al*. 2013). This double-blind, placebo-controlled trial examined exemestane as a chemoprevention agent for breast cancer in postmenopausal women. Results demonstrated exemestane administration for at least 3 years to be superior to placebo for the prevention of breast cancer in high-risk postmenopausal women (Goss *et al*. 2011, DeCensi *et al*. 2012). The incidence of breast cancer with exemestane compared with placebo was reduced by 65% (Goss *et al*. 2011, Litton *et al*. 2012). No serious toxic effects were reported with exemestane and quality of life was minimally changed, while long-term administration of tamoxifen could be associated with serious side effects such as venous thromboembolism and endometrial malignancy (Goss *et al*. 2011, Walker *et al*. 2013). An increased risk of osteoporosis with exemestane should be taken into account (Zhang *et al*. 2012). Further long-term follow-up studies are still needed.

New indications

Benign diseases: endometriosis and uterine myomas Endometriosis is an estrogen-dependent inflammatory disease associated with chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility which mostly occurs in premenopausal women (Pavone & Bulun 2012). Aromatase levels in the endometrium are elevated in women experiencing this gynecological disease and therefore, AIs could be considered as a treatment option (Bulun *et al*. 2005, Attar & Bulun 2006, Bedaiwy *et al*. 2009). Additionally, concurrent therapy such as AIs combined with progesterone or progestin, GNRH analogs, or oral contraceptives, has been suggested by several studies (Pavone & Bulun 2012). In postmenopausal women, endometriosis occurs rarely. In general, it is treated surgically because of risk of malignancy. As surgery is not always possible, systemic drugs are administered (Pavone & Bulun 2012). Treatment options are GnRH analogs, progestin, and AIs.

Several studies have indicated letrozole and anastrozole to be effective for treating endometriosis (Pavone & Bulun 2012). One case report documented therapy with exemestane in a postmenopausal woman with endometriosis, but exemestane was not able to improve symptoms. Switching to letrozole, however, relieved the pain (Mousa *et al*. 2007).

AIs can be associated with adverse effects such as osteoporosis and follicular cyst formation (Bedaiwy *et al*. 2009). Therefore, AIs are not recommended as monotherapy, but in combination with a therapy that reduces adverse effects.

Furthermore, uterine myoma is the most common benign tumor in women. Abnormal uterine bleeding and pelvic pressure often occur. The standard of care is surgery because no inexpensive and safe long-term medical treatment is available (Bedaiwy *et al*. 2009). Like endometriosis, myomas are associated with elevated aromatase and estrogen production, creating another indication to be treated with AIs. Letrozole and anastrozole have been reported to be effective at improving symptoms of uterine myomas, but, to our knowledge, no cases involving exemestane have been documented yet (Bedaiwy *et al*. 2009).

Endometrial changes One of the main adverse effects that tamoxifen-treated breast cancer patients experience is an increased risk of developing endometrial hyperplasia, polyps, and carcinoma (Fornander *et al*. 1989, Neven *et al*. 1989, Rutqvist & Johansson 2007). Patients treated with tamoxifen have a two- to three-times higher risk of developing endometrial cancer compared with individuals receiving placebo (Fisher *et al*. 1998). One study compared changes in double endometrial thickness (DET) and uterine volume (UV) between third-generation AIs and tamoxifen (Morales *et al*. 2005). DET in patients previously treated with tamoxifen was significantly higher at 3 months compared with baseline, while in patients treated with AIs no significant difference was seen. In addition, exemestane following tamoxifen treatment was found to decrease DET and UV significantly. It can be concluded that endometrial changes induced by tamoxifen can be reversed by AIs, which is a safety argument for sequential use in a curative adjuvant setting.

Conclusion

Exemestane is the only third-generation SAI. It is well-tolerated and used as a standard second-line treatment in postmenopausal patients with metastatic breast cancer.

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Additionally, its efficacy as a first choice therapy for metastatic disease has been reported. Furthermore, exemestane is considered to be a valid option for chemoprevention, presurgical treatment, or as adjuvant treatment. In the latter setting, many options are possible, including monotherapy for 5 years, tamoxifen/exemestane switch, or extended therapy with exemestane beyond 5 years adjuvant treatment. As far as anti-tumoral efficacy in advanced disease is concerned, exemestane is not totally cross-resistant with NSAIs like letrozole and anastrozole, thus yielding an additional therapeutic window of opportunity in any sequence. Moreover, they also display toxicity profiles that are not totally overlapping, useful for patients complaining of major side-effects. Importantly exemestane as its NSAI congeners may reverse tamoxifen side effects like undesirable endometrial changes and risks of thromboembolic disease. Optimal duration and scheduling still have to be explored in the adjuvant setting. In conclusion, exemestane can be considered a valuable addition to the current arsenal for the treatment at all stages of breast cancer.

Declaration of interest

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Breast cancer is the most prevalent type of cancer in women and responsible for significant female cancer-related mortality worldwide. In the Western world, over 80% of breast cancers are hormone-receptor positive for which endocrine therapy is administered. The main anti-estrogen treatments in use consist of selective estrogen-receptor modulators, such as tamoxifen, and third-generation aromatase inhibitors (AIs), such as exemestane, letrozole, and anastrozole. In this review, the focus will lie on exemestane, its clinical use, and its side-effect profile. Exemestane is the only third-generat