Chapter 12
Aromatase Inhibitors Beyond Breast Cancer: Endometrium Versus Breast Puzzle and Other Issues

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Abstract Aromatase inhibitors were developed and intended for different purposes; however, in practice they are predominantly used to treat breast cancer. It is becoming increasingly clear that this approach proves to be useful. Unfortunately, not all patients show responsiveness to this class of drugs, and some lose it over time. The expansion of the attempts to use aromatase inhibitors beyond the mammary cancer field suggests that these drugs can be beneficial in some other cancers as well as noncancerous conditions. Some of the pathological states show different degrees of resistance to aromatase inhibitors. This phenomenon warrants further studies of its causes and ways to overcome it. In this regard, noteworthy are endometrial cancer on one hand and some variants of uterine sarcomas on the other. Endometrial cancer, so as breast cancer, is referred to estrogen-dependent conditions; therefore, the markedly low responsiveness of endometrial cancer patients to aromatase inhibitors is a puzzle calling for a solution. On the other hand, some cases of uterine sarcomas show significant responsiveness to aromatase inhibitors. The reaction of these tumors is higher than in other cancer and non cancer cases studied in this regard, except for breast cancer. Taken together, this makes another incentive to study the mechanisms of resistance to aromatase inhibitors and, due to this, to expand the latter usage beyond traditional targets.

Abbreviations

AI(s)	Aromatase inhibitor(s)
BC	Breast cancer
CR	Complete response

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EC	Endometrial cancer
EMA	European Medicines Agency
ER	Estrogen receptors
FDA	Food and Drug Administration (USA)
LC	Lung cancer
OC	Ovarian cancer
OS	Overall survival
PC	Prostate cancer
PFS	Progression free survival
PgR	Progesterone receptors
PR	Partial response
SD	Stable disease

Introduction

According to recommendations approved by FDA and European Medicines Agency (EMA), the modern aromatase inhibitors (AIs) letrozole, anastrozole and exemestane are indicated exclusively for breast cancer (Table 12.1). Nevertheless, attempts continue, often on empirical grounds, to use these drugs for other indications, sometimes successfully to varying extents. In essence, the issue of why the most common use of AIs is in breast cancer rather than in any other condition hinges on the main problem addressed in this volume: what are the causes of the natural resistance to AIs and why it develops eventually after a period of responsiveness to a treatment with an AI? Analyzing the areas of AIs applicability beyond breast cancer may not only clarify what other 'non-mammary' medical fields benefit or can potentially benefit from AIs but also may provide grounds to think about what can make AIs ineffective in breast cancer. The data presented below will be distributed in two sections, one related and the other unrelated, at least directly, to oncology. Wherever a specific disease/clinical situation will be considered, available data will be provided on the activity and/or expression of aromatase, the usability of AIs, and resistance to AIs and the attempts to overcome it.

AIs in Cancer

Let's Start from Breast Cancer…

By the time of preparing this Chapter (August 2014), PubMed yielded 9187 entries in response to the query "aromatase inhibitor", and 5400 to "aromatase inhibitor AND breast cancer"; that is, breast cancer (BC) occupies about 60 % of the entire area in question. On the whole, this looks as if AIs were designed mainly to treat BC, which seems true as follows from relevant evidence [1].

Table 12.1 Approved indications for using the main inhibitors of aromatase

Drug	FDA, 2013	EMA, 2011–2013
Letrozole	Letrozole (Femara) is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early BC, for the extended adjuvant treatment of early BC in postmenopausal women who have received 5 years of adjuvant tamoxifen therapy, for first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic BC, and for the treatment of advanced BC in postmenopausal women with disease progression following antiestrogen therapy	In patients with advanced or metastatic BC, treatment with letrozole should continue until tumour progression is evident. In the adjuvant and extended adjuvant setting, treatment with letrozole should continue for 5 years or until tumour relapse occurs, whichever is first. In the adjuvant setting a sequential treatment schedule (letrozole 2 years followed by tamoxifen 3 years) could also be considered. In the neoadjuvant setting, treatment with letrozole could be continued for 4–8 months in order to establish optimal tumour volume reduction
Anastrozole	Anastrozole (Arimidex) is indicated for adjuvant treatment of postmenopausal women with hormone receptor-positive early BC, for the first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic BC, and for the treatment of advanced BC in postmenopausal women with disease progression following tamoxifen therapy. Patients with ER-negative disease and patients who did not respond to previous tamoxifen therapy respond to anastrozole rarely	Anastrozole is indicated for the treatment of advanced BC in postmenopausal women, as adjuvant treatment of postmenopausal women with hormone receptor positive early invasive BC, and adjuvant treatment of early BC in hormone receptor positive postmenopausal women who have received 2–3 years of adjuvant tamoxifen. Co-administration of tamoxifen or estrogen-containing therapies with anastrozole should be avoided as this may diminish its pharmacological action
Exemestane	Exemestane (Aromazin) is indicated for adjuvant treatment of postmenopausal women with estrogen-receptor positive early BC who have received 2–3 years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy	Exemestane is licensed for BC treatment by a national health authorities and not the European Medicines Agency

At the same time, contemplating the reasons why this design proved to be a success may help to understand why AIs fail or only partly succeed in other conditions. Therefore, periodic recurrence of the BC theme in the subsequent discussion is warranted.

Without dwelling here on using AIs in female breast cancer patients, since this issue is covered by the previous chapters, it should be noted that EMA in its relatively recent statement asserted that “it was unaware of clinical trials or specific systematic investigation—as opposed to isolated case reports—on the use of letrozole in *male* breast cancer, and that neither efficacy nor safety data exist”

[2]. The initial part of this assertion seems true; however, papers published in 2013–2014 based on observational studies and inferences from earlier findings provide for some tentative conclusions. In particular, the well-known high rates (up to 90 %) of detecting of estrogen receptors in male mammary tumors is suggested to explain the beneficial effects of AIs in such patients in the curative and metastatic setting [3]. The additional use of GnRH analogues did not increase AIs efficacy estimated by a partial response and stabilisation of disease amounting to 26.1 and 56.5 %, respectively [4]; although, according to other authors, the combination of these two types of drugs looked attractive: 10.5 % of patients had complete response, 36.8 % experienced a partial response, and 36.8 % had stable disease lasting for not less than 6 months with overall disease control rate 84.2 % [5]. With all that, there are nuances, which should not be ignored. They include still prevalent use of tamoxifen, which interferes with the effects AIs, in male BC, the need to confirm the claim that mortality rate among males treated with AIs is higher than upon tamoxifen treatment [6], and doubts concerning the ability of AIs to efficiently prevent estrogen synthesis in the testes [7]. Taken together, this introduces some uncertainty in this male vs female aspect of the issue in question, which is reminiscent of confusing differences between AIs effects in breast cancer and endometrial cancer.

Endometrial Cancer (EC)

Extragonadal estrogen production in cancer may result from either (a) preexisting aromatase activity, which was significant in the parent tissue and could become quantitatively and often qualitatively, including the genomic level, altered in the neoplastic tissue (breast cancer is a typical case) or (b) de novo aromatase activity, which emerged in the course of neoplastic transformation. The second case is exemplified, in particular, with non-small cell lung cancer (which will be addressed below) and endometrial cancer [8, 9], which is significant in that in many countries it is the most common malignancy of the female genital tract.

Aromatase determined by radiometric or immunohistochemical methods is found in EC tissues in 55–80 % of cases [8, 10, 11]. This is not significantly different from findings in BC (60–70 %) [10, 12–14], although EC and BC markedly differ in their responsiveness to AIs (see below). There is no evidence of a clear-cut association between the presence of aromatase and steroid hormone receptors in either BC or EC, save that some findings suggest that this association may be inverse, which is not accepted unequivocally [12, 15, 16]. It cannot be ruled out that the final agreement on this topic is not achieved because it is still uncertain whether aromatase and steroid receptors are colocalised in the same cells, or their interactions are mediated in an autocrine or paracrine way. Nevertheless, the concomitant presence of both ER and PR remains the main indication for the use of AIs in breast cancer. Using aromatase activity as a marker for such indicative purposes still seems unreliable [12, 17], and the suitability of aromatase mRNA and

gene polymorphisms for the same purpose still needs further ascertaining [18–21]. This issue becomes even more complicated when it comes to endometrial cancer because it is less studied, in this respect, and because of the already mentioned low effectiveness of AIs in this disease.

In this regard, it is noteworthy that the history of studies of aromatase in the endometrium was not smooth at all. By early 1980-ies, it was concluded that there is no aromatase in the normal endometrium. Subsequently, this conclusion was doubted from time to time but finally confirmed when PCR showed no evidence of $P_{450arom(CYP19A1)}$ transcripts in endometrial tissues [22], although critique of this approach may still be encountered [11]. By contrast, in endometrial cancer tissue, aromatase is found with different methods including PCR, detection of the immediate products of androgen aromatisation, detection of 'hard water' released upon aromatisation of tritiated androgenic precursors, and immunohistochemical analysis [10, 11, 23].

The present author's opinion on a potential role of aromatase in endometrial cancer was formed based on original studies carried out in the beginning of this century [24, 25]. According to data obtained paradoxically at odds with observations on blood estrogens [26, 27], a higher intratumor aromatase activity [24, 28, 29] was featured by type II rather than type I pathogenetic variant of EC [27, 30, 31]. Moreover, in poorly differentiated tumors (G3) this increase was pronounced enough to suggest that aromatase is involved in the unfavorable clinical course of EC and thus may be used to predict such cases [24, 28]. Independent data either lend support to this observation [32, 33] or contradict it [11, 34] warranting further studies. Interestingly, in a study carried out in collaboration with the Laboratory of Molecular Oncology headed by Prof. Imyanitov, it was found that, among type II compared with type I EC patients, the bearers of the A6A6 allelic variant of aromatase (CYP19), which points at potentially higher activity, are detected more frequently [29]. It can be added that studied intronic TTTA(n) repeats of CYP19 vary in number from 1 to the ≥7, and bearing of genotypes with longer alleles (like A6A6 or A6A7), obviously, can lead to hyperestrogenization; this is confirmed also with higher lumbar spine bone mineral density and lower risk of spine fractures [35].

The polymorphisms of another steroidogenic enzyme, 17α-hydroxylase/17, 20-liase (CYP17), which is implicated in the synthesis of the androgenic precursors of estrogens, showed no difference in their occurence in type I and type II EC patients [29]. At the same time, although EC patients who bore different CYP17 polymorphic variants did not differ in their blood steroids, including estradiol, testosterone and dehydroepiandrosterone sulfate, the homozygous A2A2 bearers (the most rare variety) featured, as contrasted to A1A1 homozygotes and A1A2 heterozygotes, the lowest basal and reactive—i.e., after glucose load—blood insulin [36]. The latter observation can be put in association with the evidence that, although decreases in endometrial M-echo signal and increases in FSH and LH concentrations after neoadjuvant treatment with AIs were more pronounced in type I patients, decreases in tumor PgR content ($p = 0.04$) were more revealing in patients with type II EC. Besides, decreases in aromatase activity in tumor

tissue at the end of such treatment were found predominantly in patients with lower body weight (BMI < 27.5) [24], which can be associated with the aforementioned decreases in blood insulin [36]. Thus, although type II EC is often believed to be hormone-independent, the high rate of estrogen biosynthesis in such tumors may prompt a reconsideration of this belief [24], as also follows from the recent evidence that the risk factors of type I EC and type II EC are rather close [37]. Altogether, the above highlights such questions as which EC patients will benefit from taking AIs and what is currently known about the therapeutic efficiency of AIs in EC.

In reviewing any evidence relevant to this, one should bear in mind that, by contrast to BC, EC is a disease where adjuvant hormonal therapy (with progestins as the primary option) did not show any significant effect and, therefore, is virtually never used at present [38]; the factor of patients' selection probably needs to be studied additionally, though [39]. This seems also to be true with respect to AIs, although only a few relevant studies on small patient samples are available. For example, in a trial carried out at the Tom Baker Cancer Centre in Calgary (Canada) it was possible to assess the effectiveness of therapy with AIs, mainly nonsteroidal, in 7 patients only. Partial response was observed in 1 (14 %), stable disease in 5 (71 %), and progression in 1 (14 %) of the patients. Taking into account that in a larger sample where objective results were not available but subjective improvement was reported in 70 % of cases, the authors concluded that AIs can be used as a potential therapy in patients who have a contraindication to surgery or in whom therapy with progestins either have failed or cannot be used [40]. It is worthy to add, although this information is somewhat oblique, that gynecological abnormalities were assessed in the ATAC trial where BC patients received adjuvant tamoxifen, anastrozole (Arimidex) or a combination thereof. After 2 years of treatment, endometrial thickness remained within 5 mm (baseline: 3.0 mm) in patients treated with anastrozole, increased by 3.2–7.0 mm in patients treated with tamoxifen, and showed a similar trend in the combination group [41]. After 6-years follow-up, there were non-significantly fewer endometrial abnormalities with anastrozole than with tamoxifen (12.4 % vs. 20.2 %, odds ratio 0.52; $p = 0.17$); however, the effect of drug combination was not traced because this arm of the trial was discontinued [42]. On the whole, there are no grounds so far to claim a protective (antiestrogenic) effect of anastrozole on the endometrium.

Back to progestins already mentioned above, these are the drugs that should be rated as the most effective (responses were seen in 60 % of cases) neoadjuvant therapy for EC [43–45]. By now, only a few attempts to use AIs in this setting have been reported. In one such study, ten previously untreated postmenopausal patients (mean age 59 years) with endometrial cancer, predominantly stage I disease, received letrozole 2.5 mg/day for 14 days before surgery. The treatment was well-tolerated in all patients. In two patients, pain relief in the lower part of the abdomen and/or decrease in intensity of uterine discharge were reported. In three of the ten cases, substantial decreases in endometrial M-echo (ultrasound) signal, on average by 31.1 % versus baseline values, were noted [46]. Figure 12.1, which presents these and some other results of this work graphically, shows that,

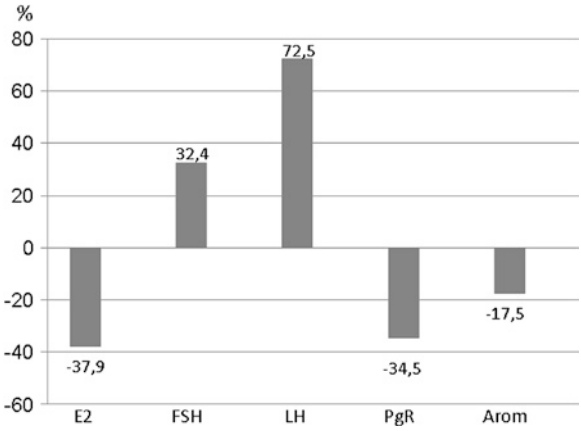

Fig. 12.1 Trends of the changes (%) in parameters studied before and after neoadjuvant therapy of endometrial cancer with the aromatase inhibitor letrozole (constructed from the data presented in [24, 25, 46]). E2, FSH, and LH: serum levels of estradiol, follicle-stimulating and luteinising hormone; PgR and AROM: tumor tissue progesterone receptor level and aromatase activity

during treatment, the mean blood estradiol decreased by 37.9 % and FSH and LH increased by 32.4 and 72.5 %, respectively, whereas the mean tumor tissue progesterone receptor (PgR) level decreased by 34.5 %, and aromatase activity only by 17.5 %, the latter decrease showing no correlation with changes in the endometrial M-echo signal [47].

As a follow-on of the above study, the effects of neoadjuvant letrozole where compared with those of anastrozole (n = 15, 1 mg/day, 28 days) and the non-steroid AI exemestane (n = 13, 25 mg/day, 14 day) [25]. Endometrial wall thickness (M-echo signal) decreased in 60 % of patients treated with anastrozole, in 58.3 % with exemestane, and in 30 % with letrozole. The differences might be attributed to treatment duration, which was longer with anastrozole, as well as to the steroid vs. nonsteroid nature of the drugs used. The latter possibility is consistent with that progesterone receptor downregulation in EC tissue (a marker of attenuated estrogenic stimulation) was most expressed with exemestane [25]. As an additional comment, the duration of the above neoadjuvant treatment with AIs was deliberately limited to one month, whereas the recommended duration of same therapy for breast cancer is 3–4 months, and proposals to increase in up to 7.5 months [47] have been repeatedly put forward.

To complete the consideration of neoadjuvant AIs in EC, the recent trial carried out at St. James University Hospital (Leeds, UK) [48] included 24 patients (mean age about 63 years) randomized into two groups: 16 patients received anastrozole (1 mg/day, 11–49 days, 20 days on average) and 8 patients received placebo (13–48 days, 23 days on average). Steroid receptors, Ki-67 antigen, and Bcl-2 protein were tested separately in endometrial glands and stroma. Anastrozole therapy resulted in a significant decrease in Ki-67, which was less pronounced in glands than in stroma, and significant decreases in ERα and androgen receptor in glands, whereas PgR (in contrast with [25]) and the apoptosis marker Bcl-2 were virtually unchanged. The authors acknowledged the importance of the decrease in the proliferation marker Ki-67 and provided no explanations to decreased ERα and unchanged PgR expression and no data about the EC course [48].

Clinical information proper may be found so far only in the results of using AIs in disseminated and recurrent/metastatic EC. The available evidence is summed up in Table 12.2, which presents data provided by three studies carried out 8–14 years ago [49–51] and in two recent publications: an original paper [52] and a review [53]. The evidence suggests that, despite of the good tolerability of these medicines, the overall response (CR + PR) in EC is 8.7–11.8 %, which is by 3.5–5-fold inferior to AIs effectiveness in BC in similar clinical settings [5, 54, 55].

Now, what is the cause of the relatively low responsiveness or high resistance of EC to AIs? What stands behind the resultant paradox based on the claims that estrogen dependence is repeatedly found in EC [27, 31]? With all the many approaches to answering these questions, the final solution is not yet known. Some tentative explanations should however be mentioned. Most importantly, no matter how prosaically it sounds, the mammary epithelium and the endometrial epithelium are two different epithelia. Differences between them encompass the discordant effects of progestins, tamoxifen and other hormone-associated factors, as summed up in Table 12.3 without citing extra literature, which is exceedingly vast. The possible causes of these differences may include the tissue-specific characteristic of the receptor apparatus and its coactivator and corepressor systems, signal transduction mechanisms, in particular peptide signalling, and the alternative promoters of aromatase gene expression [1, 8, 54, 56]. These factors are much more thoroughly studied in BC [21] thus delineating an enormous field of research related to EC and other potentially estrogen-related cancers as well as non-cancer pathologies [56, 57].

Ovarian Cancer

Whereas EC is the most frequently occurring tumor among gynecological malignancies, ovarian cancer (OC) is considered to be the most lethal, which explains so much effort devoted to searching for an effective therapy for this disease. Along with surgery, radiotherapy and chemotherapy, which remain the primary treatments for ovarian cancer, different endocrine therapeutic approaches were also tried for decades. Turning to AIs in these attempts may be explained by three considerations, at a minimum: the known roles of estrogens in OC pathogenesis, the discovery of steroid hormone receptors in the epithelial ovarian carcinomas, and the presence of aromatase in these tumors [58–62]. There is still no full consensus on the above, including possible therapeutic options. For example, aromatase activity in the tissues of normal ovaries, ovarian cysts and ovarian cancer was found to negatively correlate with ERα expression, which was the highest in the normal ovarian epithelium ($r = -0.34$, $P < 0.001$). At the same time, aromatase activity did not correlate with OC stage, grade and histological type and with patient survival [60]. Nevertheless, endometrioid ovarian carcinomas, which contain ER, are still believed to be the OC most likely to show beneficial effects upon therapy with AIs.

Table 12.2 Effectiveness of aromatase inhibitors in disseminated and recurrent endometrial cancer

Publication type	Drug	Regimen	Clinical effect	Reference number
Original study: 23 patients (9 cases with G3 tumor)	Anastrozole	1 mg/day, not more than 28 days	2 PR (8.7 %), 2 SD (8.7 %), mean PFS 6 mo	Rose et al. [49]
Original study: 32 patients (9 patients after progestin therapy); PgR and ER are found in 86 % of tumors	Letrozole	2.5 mg/day (until progression)	1 CR, 2 PR (9.4 %), 11 SD (34.3 %) mean PFS 8.8 mo	Ma et al. [50]
Original study: 28 patients (17 with ER + tumors)	Exemestane	25 mg/day (until progression)	In ER + tumor cases: 1 CR, 1 PR (11.8 %), 6 SD > 6 mo (35.3 %)	Nordstrom et al. [51]
Original study: 51 patients with advanced (FIGO stage III-IV) or relapsed EC (39 ER + tumor cases)	Exemestane	25 mg/day (until progression)	In the ER + patients: an overall response 10 %; a lack of progression after 6 mo in 35 % of the patients. No responses were registered in the ER-negative patients. In the ER + group OS was 13.3 mo, in the ER– group it was 6.1 mo	Lindemann et al. [52]
Review: advanced or recurrent EC	Third generation AIs		Response rates within 10 %	Lee et al. [53]

Notes CR complete response, *PR* partial response, *SD* stable disease; *PFS* progression-free survival; *OS* overall survival time

Table 12.3 Some hormone-associated distinctions between endometrial and breast cancer or respective normal tissues (according to available literature, references in the text; see also [130])

Feature	Endometrial cancer (endometrium)	Breast cancer (mammary epithelium)
Risk associated with estrogen replacement therapy in the menopause	Higher	Lower
Estrogen deficiency-associated femoral neck fracture rate in case histories	Lower	Higher
Mitotic index	Higher in the follicular phase of menstrual cycle	Higher in the luteal phase of menstrual cycle
Tamoxifen effect	Typically estrogenic	Antiestrogenic
Tissue estrogen level	Higher	Lower
Tobacco smoking effect on incidence ("antiestrogenic" effect)	More pronounced	Poorly pronounced
Diabetes mellitus	Risk factor in postmenopausal and reproductive period	Is found more often in post-menopausal period
Obesity	Prevalence in reproductive ages in not less than in post-menopausal females	Risk factor in postmenopausal variant of disease
Preventive effect of peroral steroid contraceptives	Pronounced	Not shown
Progestin use in endocrine therapy of disseminated disease	First-line therapy	Third- or fourth-line therapy (used rarely at present)
AIs use in therapy	AIs are still virtually unused	AIs use is prevalent and rather often effective

In practice, AIs have been used never as the first-line therapy for OC and, usually, supplement other chemotherapeutic drugs, such as platinum preparations and taxanes, are prescribed when other treatments for advanced or recurrent OC fail. The accumulated experience may be exemplified with several most recent publications, leaving aside the literature published since 1990-ies through the first decade of the present millenium. The most systematic review of recent findings is provided by Modugno et al. [63] who discuss the results presented in seven papers, which altogether cover the outcomes of treatment of 264 patients having persistent or recurrent OC, of whom 53 were treated with anastrozole, 22 with exemestane, and 189 with letrozole. Outcomes included only one CR case (0.3 %), 20 PR cases (7.6 %), and 81 SD cases (30.7 %). Having agreed with other authors in that the effectiveness of AIs is low in OC and even somewhat lower than in EC, Modugno et al. [63] also share the view that among OC patients there are always a few of those who can show more beneficial responses to AIs. Indeed, in their recent review van Meurs et al. recalled data on rather good responsiveness to AIs of granulosa cells ovarian tumors [64]. Therefore, what is needed is to select patients and

find predictive markers of responsiveness to AIs and/or the ways to escape resistance to them in OC, which is, naturally, a part of a broader agenda.

Here it is worthy to mention two more points that may, at least indirectly, be of relevance to OC proper. One of the points is a certain degree of similarity between the pathogenetic pathways of OC and endometriosis, which involve aromatase, sex steroid receptors, and some growth factors [65]. If confirmed, this might be important by providing some practical hints because the responsiveness of endometriosis foci to AIs is known to be higher than that of OC (see below). The second point is that many OC patients bear BCRA1 mutations [66], which are associated, similarly to decreased BCRA1 expression, with aromatase upregulation [67, 68]. Therefore, the possibility that OC patients who have BRCA1 mutations are most responsive to AIs cannot be ruled out and warrants special studies.

Lung Cancer

According to SEER data, more than 255 thousand newly detected lung cancer (LC) cases or about 14 % of all new cancer cases were expected to occur in the USA in 2013. In addition, LC-related death rate being twice as high as caused by all cancers and making 27.5 % of all cancer-related deaths, evidencing the high prevalence and severity of the disease [69]. Among all LC cases, 80–90 % are attributed to non-small cell carcinoma, including squamous cell carcinoma, which is often found in tobacco smokers, and adenocarcinoma, which is more prevalent in women. Although males are more vulnerable to LC than women are, females in many countries are gradually catching up, possibly because of changing smoking patterns and other factors, including endocrine ones.

Initially, the endocrine factors of LC development were generally thought to be limited to corticosteroids and their metabolites, although papers that suggest a potential role of estrogens in LC have been published since almost half a century ago [70]. Interest to this problem is on the rise since 1990-ies, particularly over the last 10–15 years, when the terms “aromatase” and “aromatase inhibitors” started to appear increasingly in publications relevant to LC. The idea emerged that estrogen replacement therapy during the menopause can influence LC risk and LC-related mortality in female smokers [71, 72] and that PgR and ER, especially ER-beta, found in lung cancer tissue may be involved [73, 74]. Noteworthy in this regard is that ER-beta in lung cancer tissue is often coexpressed with aromatase, and this combination is associated with a lower survival in male, but not female, LC patients, which suggests the feasibility of selective endocrine therapy, based on assessing these markers [75].

The ‘self-sufficient’ significance of aromatase activity in the lung tumor tissue, particularly in the non-small cell cancer, was assessed in a number of works. In some of them the association of a lower activity with a better survival was noted suggesting that aromatase activity can be among prognostic markers and that it is reasonable to try AIs as a therapy for LC [76, 77]. The latter suggestion is

supported by experiments showing that in nude mice with A549 lung tumor xenografts, administration of anastrozole for 21 days elicited pronounced inhibition of tumor growth in vivo [78]. No relevant clinical data are available by now; however, AIs are combined with estrogen receptors down-regulators in some ongoing Phase I-II clinical trials conducted among patients with advanced LC [77, 79]. Another therapeutic option in LC may be to combine an AI with an EGRF inhibitor as prompted by the experiments where the EGRF inhibitor gefitinib was given together with the pure antiestrogen fulvestrant [79, 80]; of note, though, no association between EGRF mutations and ER-beta expression was found in LC tumor tissue [81]. If mentioned approaches prove to be clinically beneficial, a certain similarity between LC and BC would be confirmed [82] promoting AIs expansion to therapies for cancers that feature unconventional hormone dependency patterns.

Other Tumors

It makes sense to begin this section with uterine sarcoma because, first of all, it is often reported to show beneficial responses to AIs. Sarcomas of the uterus are mesenchymal tumors with a poor prognosis and aggressive biology, although some of their forms are more differentiated and less aggressive. The recent review [83] contains reports about 7 cases (4 endometrial stromal sarcomas and 3 leiomyomas) treated by its authors with AIs. Besides, independently published papers are reviewed to cover 11 similar treatment reports and 6 retrospective studies. Taken together, this evidence suggests that the overall response rate of endometrial stromal sarcoma to AIs was 67 % [CR 7 % and PR 60 % (!)], and the partial response rate of leiomyosarcoma to AIs was 11 %, with no reported CR's [83]; however, in the ongoing Phase two clinical trial using letrozole to treat ER + or PgR + uterine leiomyosarcoma patients, somewhat more encouraging results are expected [84]. Since endometrial sarcoma responses to AIs are reported to be not inferior (if not superior) to responses to progestins [83], further studies are warranted to elucidate the causes of this fairly high responsiveness to AIs.

Prostate cancer endocrinology has been long centered 'around androgens'; however, due to studies carried out over the last decades, estrogens too are increasingly recognised as factors influencing prostate cancer development and progression [85]. With regard to a potential role of aromatase inhibitors, several findings and hypotheses deserve attention. In particular, aromatase is thought to be significant for balancing androgens and estrogens in prostate tissue as well as for mediating its diseases [86, 87]. More fundamental aspects of the prostate biology and carcinogenesis may relate to ER-containing stem/progenitor cells functioning [87], aromatase activation by prostaglandin E2 in the stromal cells [88], and the long standing idea advocated by Bosland that estrogens and androgens are synergetic in producing carcinogenic effects mediated by the catecholestogens' metabolites-DNA adducts in prostate [89]. Because AIs inhibit the synthesis of the classic estrogens and thus limit the generation of the progenotoxic metabolites of

estrogens, the above idea is interesting from the point of view of using AIs for PC prevention, which could be the objective of special investigation, at least in an experiment. In clinics, to the best of our knowledge, the use of modern AIs in PC has been limited (in spite of the above) to eliminating, albeit less efficient than with tamoxifen, of gynecomastia and breast pain in patients treated with antiandrogens [90] and to the old-established recommendation of aminoglutethimide combined with hydrocortisone for hormone-resistant PC [91]. In the latter case, remission based on laboratory findings (PSA level) was reported in 37 % of patients, median PFS in responders being 23 months [91]; however, this study had no continuation.

Of the other cancers, a high aromatase activity in melanoma tissue has once attracted attention [92]; however, aminoglutethimide proved to be inefficient in patients with this tumor [93]. There were no attempts so far to use AIs with the aim to treat patients having cervical cancer or tumors of the thyroid gland, colon or liver; however, the reasonability of such attempts deserves consideration in view of arguments presented in the number of papers [94–97]. In particular, there is some evidence that estrogens are involved in the promotion and, probably, even initiation of tumors in the liver and thyroid [98, 99].

Meanwhile, interests of researchers and clinicians expand to estrogens and to aromatase inhibitors for treatment of several non-cancer conditions which will be discussed further.

Non-cancer Conditions

Endometriosis

The prevalence of endometriosis in the general female population is 7–10 %, and may be up to 30–35 % in infertile women [100]. Clearly, to find successful therapies for this condition is an important task. In-depth studies of aromatase activity, expression and regulation in endometrioid lesions provided a large body of evidence suggesting an important role of estrogen synthetase in the pathogenesis of endometriosis and in the development of different variants of its clinical course and localisation, including the involvement of peritoneum and ovaries. In endometriosis, aromatase expression is primarly controlled by the proximally located promoter 1.3/II [8], which is regulated by a number of factors, such as prostaglandin E2 and peroxisome proliferator activated receptor-γ coactivator-1α (PGC-1α), assisted by auxiliary mediator [101, 102]. These and related findings make grounds for publications where AIs are proposed as therapeutic means for endometriosis, which can be no less potent than the conventionally used progestins, peroral steroid contraceptives etc.

In particular, it has been repeatedly observed that AIs prescribed to endometriosis patients of reproductive ages attenuate and, at times, eliminate for a while painful sensations associated with endometriosis as discussed in the comprehensive

reviews [103, 104]. In premenopause the effects of AIs have to be potentiated by other therapies [104], whereas in the postmenopausal endometriosis, AIs by themselves can be effective and even can reduce endometriotic lesions [105]. At the same time, there are publications where the reasonability of using AIs in therapies for endometriosis is disputed and the need for further studies is advocated [106, 107]. It is also noted that, in treating endometriosis with AIs, one should mind side effects, primarily a trend to decreased bone mineral density [104], which has been intensively studied in breast cancer field. It is also suggested to conduct more studies aimed at examining pregnancy rates and outcomes after AIs have been used to treat endometriosis [104], which seem important in view of the aforementioned association of endometriosis with infertility.

Infertility

Reproductive health problems occupy a special place in the attempts to use AIs outside the breast cancer area as will be relatively briefly reviewed in this and the subsequent sections.

Besides the above observations that the successful treatment of endometriosis with AIs can improve fertility in patients younger than 30–40 years, attempts were made in the recent years to use AIs to achieve the same result in other clinical situations, including unexplained infertility, infertility associated with the use of gonadotoxic therapy in cancer patients, and in male infertility. In women, AIs are used to induce ovulation in anovulatory states, including in vitro fertilisation (IVF) cycles, either independently or as an auxiliary to clomifen citrate and gonadotropin preparations as discussed in a recent Cochrane review and other publications [108–113]. Conclusions from the available evidence are sometimes unequivocal. Thus, it is not well known whether letrozole or other AIs can be used for this purpose independently (that is, as an only treatment). Also, the studies are in progress which will be helpful in understanding whether the total dose of gonadotropins should be modified upon their use in combination with AIs, whether there are differences in the use of letrozole in noncancer patients and after gonadotoxic therapy courses in cancer, and finally whether AIs or more conventional therapeutic modalities used to induce ovulation produce comparable results, including pregnancy rate etc. However, the consensus is that, in order to expand options available to treat infertility, it is reasonable to go on with trials including the use of combinations of AIs with other drugs, such as the antidiabetic biguanide metformin widely utilized in polycystic ovarian disease [108, 109, 112]. Among advantages of AIs relatively low cost and lower multiple pregnancy rates are mentioned, while limited data are presented on their potential teratogenic effects as well as on oocyte and embryo quality [113, 114].

There are reports on the attempts of using AIs to treat male infertility caused by impaired spermatogenesis. Anastrozole (1 mg/day) or letrozole (2.5 mg/day) administration has been reported to increase spermatozoid counts and blood

testosterone/estrogen ratio; however, it is still unclear whether oocyte fertilization is really improved in these cases [115].

Medical Abortion

In recent years AIs attract attention as a means for not only induction of ovulation but, on the contrary, for termination of pregnancy. This trend may be exemplified with a study where 20 women scheduled for abortion at 2 months of gestation received letrozole (10 mg/day) for 7 days and intravaginal misoprostol (prostaglandin E1) on the 7th day. Abortion was reported to be induced in 95 % women (95 %) at 7.5 h on average after misoprostol administration. Subsequent interviews showed that 17 women (88 %) would prefer this mode of abortion on a possible necessity in the future [116]. Importantly, letrozole used in such settings does not influence uterine contractility, and its abortion-inducing effect is mediated via estrogen production and metabolism [117].

The possible contraceptive effect of letrozole in women is contemplated tentatively because of its impact on luteal function [118].

Gynecomastia

Gynecomastia sometimes occurs in adolescents during normal maturation, but more often results from diseases associated with a disbalance between estrogens and androgens, such as upon liver cirrhosis, or from some medications. The latter may be categorised into two groups: cardiovascular drugs, including calcium channel blockers, angiotensin-converting enzyme inhibitors, spironolactone, etc., and drugs used to treat prostate cancer, including estrogens and antiandrogens. One of the causes of gynecomastia is the aromatase excess syndrome, a rare hereditary disorder manifested in the pre- or peripubertal period [119]. AIs have been used in a number of the above conditions, including excessive aromatase activity where AIs can be quite effective, liver cirrhosis-associated gynecomastia where AIs are most likely to be not inferior to tamoxifen, and antiandrogen-induced gynecomastia where AIs are less effective than tamoxifen is [1, 119, 120].

Other Conditions

A non-exhaustive list of additions to the above includes the attempts to use AIs in adolescents to prevent premature epiphysis closure in pubertas praecox and in other growth disorders [121]. It is still unclear, whether AIs can be used instead of testosterone substitution therapy for late-onset hypogonadism in elderly males

[122]. In children, AIs were tried in Peutz-Jeghers syndrome (autosomal dominant genetic disease characterized by the development of benign hamartomatous polyps in the gastrointestinal tract and pigmented macules on the lips and oral mucosa, sometimes associated with aromatase excess), McCune-Albright syndrome (a genetic disorder of bones manifested also in skin pigmentation and hormonal problems along with premature puberty), and in some forms of hyperandrogenism, including testotoxicosis and congenital adrenal hyperplasia [123].

As to women, noteworthy is the idea to use AIs to treat uterine myomas. In scarce reports about such attempts, more or less optimistic conclusions can be found. An optimistic publication reports about 30 premenopausal women aged 30–55 years having uterine myomas sized within 4 cm who received 2.5 mg of letrozole daily for 12 weeks. Myomatous nodes shrinked, on average by 1 cm in size and by twofold in volume, by the end of the 3rd month of the treatment. No changes in blood lipids and testosterone, FSH, LH and even estradiol were noticed (although the so-called rebound phenomenon might be expected in these cases); the most pronounced adverse effects being nausea and hot flushes [124]. On the other hand, in a Cochrane review on this subject [125] it was concluded that the trend to myoma shrinkage, although noticeable, is not always significant and that studies included only small samples of patients and were not blinded. Further studies are needed in this so as in several other cases discussed above.

Conclusions and Perspectives

The evidence discussed in the present chapter and generalized in Fig. 12.2 suggests that aromatase inhibitors can be used with broadly varying effectiveness for indications other than breast cancer, in conditions not limited to neoplasms, and in patients ranging from children to elders.

The causes of therapeutic failures with AIs are not always clear. They may relate to the tissue-specific features of the aromatase complex and its regulation as well as be disease-specific. Still poorly developed are approaches to escaping resistance to AIs, e.g. in EC, and to increasing responsiveness to AIs in conditions including non-cancer pathologies.

These are the problems to be tackled in the nearest future, in particular, by ascertaining which patients are most responsive to AIs, and by finding most appropriate combination of AIs with other drugs able to potentiate the effects of AIs in each specific indication. Such combinations may include cyclooxygenase inhibitors; however, their effects in experimental endometriosis were opposite to what was expected [126]. Combinations of AIs with the antidiabetic biguanide metformin, which is remarkable in its multisided effects, are already being tried in BC [127] and used in polycystic ovarian disease and other conditions associated with infertility [112].

The factors that limit the long-term use of AIs in cancer and non-cancer conditions include side effects, such as decreased bone mineral density, hyperlipidemia,

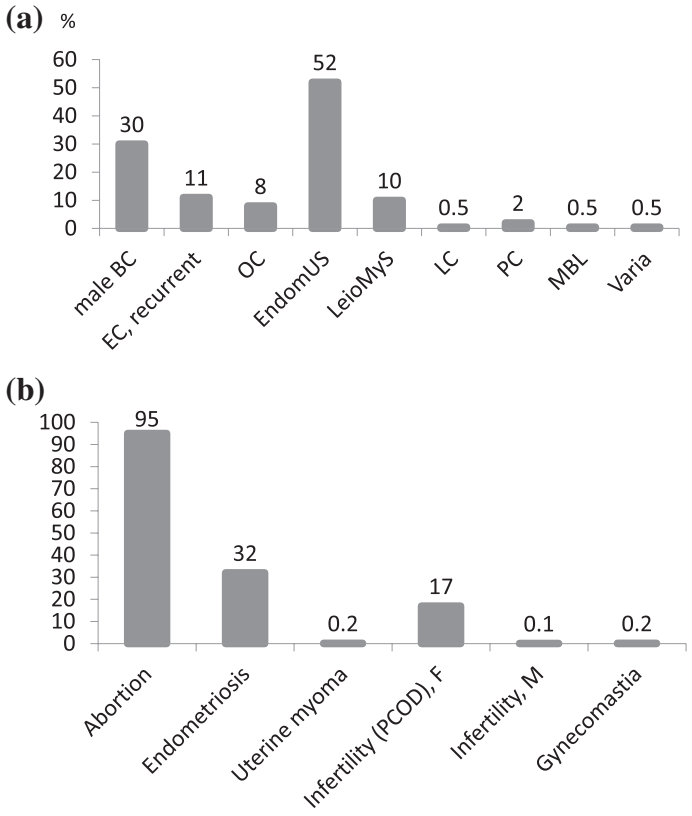

Fig. 12.2 The use and effectiveness of aromatase inhibitors in different medical fields (except female BC), contemporary situation (please see text for additional explanations, some data need confirmation). **a** Oncology: partial response rates (%) to AIs in various indications. *BC* male breast cancer; *EC* endometrial cancer, recurrent; *OC* ovarian cancer; *EndomUS* endometrial uterine sarcoma; *LeioMyS* leiomyosarcoma; *LC* lung cancer (no reliable clinical data with AIs so far); *PC* prostate cancer (AIs were used mainly for the alleviation of breast events in patients treated with antiandrogens); *MBL* melanoma (attempts to use AIs are rare and not successful); Varia: cervical, hepatocellular, thyroid, and colorectal cancer (only assumptions, no clinical or experimental data). **b** Non-cancer clinical conditions: success rates (%) for various indications. Medical abortion induction: of usage of AIs in combination with prostaglandin E1. Endometriosis: mainly alleviation of pain. Uterine myoma: solitary attempts to decrease myoma size were performed. Infertility: treatment attempts were made more often and were more successful in females (f.e. in polycystic ovarian disease, PCOD) than in males; randomized studies were carried out rarely so far. Gynecomastia: effects are disease type-dependent and so far most promising in cases of aromatase excess

and cardiovascular events, which must be taken seriously. Developing of means able to prevent these side effects may result in increasing the number of patients electable for being treated with AIs. At the same time, the endocrine side effects of AIs may be used as predictive factors of responsiveness to AIs in cancer patients [128, 129] and as such warrant confirmation and application beyond oncology field.

On the whole, with regard to a more general objective of this chapter, it could be summarised that estrogens, along with being potent mitogenic factors in breast, have a broader range of targets and effects in human physiology and pathophysiology. This warrants a persisting interest to the details of biosynthesis of these hormones and to means, including AIs, able to modify estrogen biosynthesis and (due to this) effects in cancer and in other diseases and clinical situations.

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