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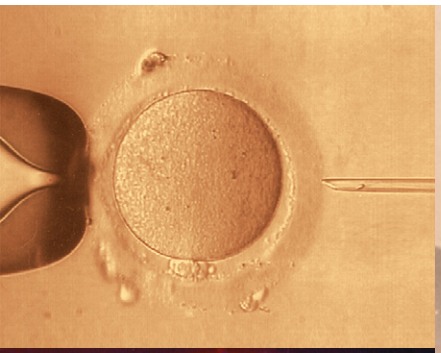

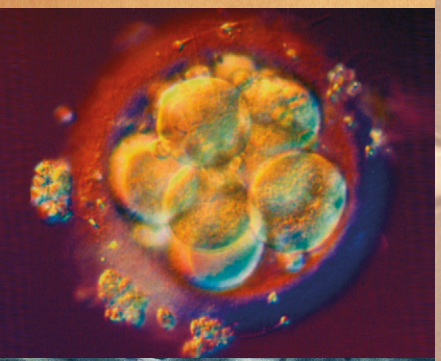

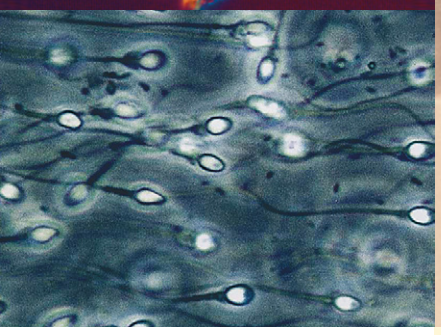

Update on Aromatase Inhibitors

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Update on Aromatase Inhibitors*

V. Seifert-Klauss[1], T. Rabe[2], A.-K. Krämer[3], A. Schneeweis[4]

Aromatase inhibitors (AI) block the last phase of estrogen production in many types of tissues which express the enzym aromatase, among them muscle, liver, adrenal, brain and fat. The enzyme catalyzes the last step of the biosynthesis of the estrogens, i. e. the aromatisation of testosterone to estradiol and of androstendion to estrone. Aromatase is localized in the membrane of the endoplasmatic reticulum and is also produced in the placenta and the gonads. Mutations in the gene CYP19A1, which codes for aromatase, can lead either to lack or excess of aromatase. Gene polymorphisms also influence the amount of bioavailable estrogen and bone density.

Indications: AI are approved for the treatment of postmenopausal women with hormone receptor positive breast cancer, both in the adjuvant setting as well as after recurrence and in progressive disease.

In premenopausal and in perimenopausal women AI cause an increased sensitivity of the ovaries to follicle stimulating hormone (FSH) and can thereby lead to a boosted estrogen answer – this effect is particularly pronounced in early perimenopausal women – so that these situations demand a combination with GnRH-analogue if AI treatment is to be initiated. Alternatively, tamoxifene may be used in premenopausal patients, with or without GnRH analogues. Treatment of premenopausal patients with hormone receptor positive breast cancer with aromatase inhibiting therapy alone constitutes an absolute contraindication. Aromatase inhibitors do not lead to estrogen receptor downregulation or block the receptor such as tamoxifene. An exceptional application is the application in reproductive medicine in women who do not have hormone receptor positive breast cancer: because of the higher sensitivity induced by AI-co-therapy, FSH-doses and -costs for assisted reproduction are reduced, and ovarian hyperstimulation syndrome (OHSS) may be avoided.

For premenopausal diseases which are said to be positively affected by estrogen withdrawal, such as endometriosis or fibroids, studies have not shown any significant advantage of AI-therapy so far. Bodybuilders use AI inhibitors to prevent estrogenic side effects of a testosterone therapy through conversion in estrogens and to enhance testosterone levels by blocking its metabolisation. Medical application of AI is discussed for boys with short stature as a more cost-effective alternative to treatment with human growth hormone.

Substances: Currently, the 3 commonly used AI are anastrozol, letrozol (both non- steroidal, displaying competitive binding and reversibleinhibition) and exemestane (steroidal, inactivation of aromatase through covalent binding), show better anticancerous effects compared with tamoxifene.

Effects: AI decrease estradiol serum levels in postmenopausal women from around 30 pmol/l to < 3 pmol/l. Intracellular estrogen-concentrations are reduced, too. Under adjuvant therapy (early breast cancer), this estrogen withdrawal prolongs the time to recurrence, and results in higher rates of disease free survival (absolute reduction of 2.7% after 5 years compared with tamoxifene) while the 100-months-analysis of the ATAC-trial did not find an effect on overall survival (ATAC trialists group).

In the metastasized situation, a Cochrane-Review-metaanalysis of 31 trials on AI in a total of 11.403 postmenopausal patients with advanced disease showed statistically significant improved survival under AI of 10% in comparison with the other endocrine therapeutic options tamoxifene (TAM), megestrolacetat (MA) and medroxyprogesterone acetate (MPA) (HR 0.90; 95-%-CI: 0.84–0.97).

Side effects: The most common side effects are hot flushes, joint and bone pain, reduction of bone density, diarrhea and rashes. In women with increased risk for osteoporosis the fracture rate is higher under AI than with the SERM tamoxifene, so that before initiating therapy, a bone density measurement is recommended.

Modes of treatment in breast cancer: Adjuvant therapies with AI include monotherapy over 5 years (in postmenopausal women), combination with GnRH-analogue (in women who are not postmenopausal) and also the switch-concept (2 years of tamoxifene, followed by aromatase inhibitor for 3–5 years or vice versa. High risk situations may warrant „extended use" with continuation of the therapy after 5 years (up to 10 years).

In the metastasized situation, AI are applied in first- as well as in second-line therapy, if there is not a rapid disease progression in vital organs (lung, liver), or as maintenance therapy after chemotherapy. As in the adjuvant setting, in premenopausal women AI must be combined with GnRH analogues.

For postmenopausal women with Her2 neu-positive carcinomas, a combination therapy of aromatase inhibitors with trastuzumab or lapatinib has recently been approved. For Her2 neu-negative, hormone receptor positive disease, a combination of exemestane with the m-TOR inhibitor everolimus can be applied after failureof aromatase monotherapy with non-steroidal AI.

*Future perspectives:*The combination of aromatase inhibitors with the anti-estrogen fulvestrant was not more effective than each substance on its own (SoFEA investigators). Further ongoing trials explore the combination of aromatase inhibitors with neutralising antibodies against IGF-1 or its receptor (e.g. ganitumab), metformin and inhibitors of PI3k and/or Akt. Some of these targeted therapy approaches try to overcome resistance to endocrine therapy, e. g. combinations with mTOR inhibitors are being investigated in clinical trials. Also, the inhibition of PI3k and the new class of CDK4/6 inhibitors represent new promising approaches of combination therapy with aromatase inhibitors. **J Reproduktionsmed Endokrinol_Online 2015; 12 (4): 353–9.**

Key words: aromatase inhibitors, breast cancer, endocrine therapy, side effects, clinical management

Introduction

The enzyme aromatase catalyses the last step of steroidal synthesis in vertebrates, namely the transformation of testosterone into estradiol and of androstendione to estrone (aromatisation). The aromatase coding gene, CYP19A1, is located in the membrane of the endoplasmatic reticulum and is produced in the liver, adrenal glands, fat tissue, in the brain, the placenta and in the gonads. Mutations in the CYP19A1-gene can lead to heritable lack or excess of aromatase [1] (Fig. 1).

Aromatase inhibitors (AI) (Fig. 2) block the last phase of estrogen production in many types of tissues which express the enzym aromatase, among them muscle and fat and are approved for the treatment of hormone sensitive breast cancer in postmenopausal women.

As AI in perimenopausal ovaries can potentially increase the endogenous levels of estradiol, AI are only suitable for certainly postmenopausal women, after ovarectomy or under simultaneous blockade of ovarian function with e. g. GnRH analogues.

Further fields of indication – apart from breast cancer – for which AI were discussed in premenopause or even for chil-

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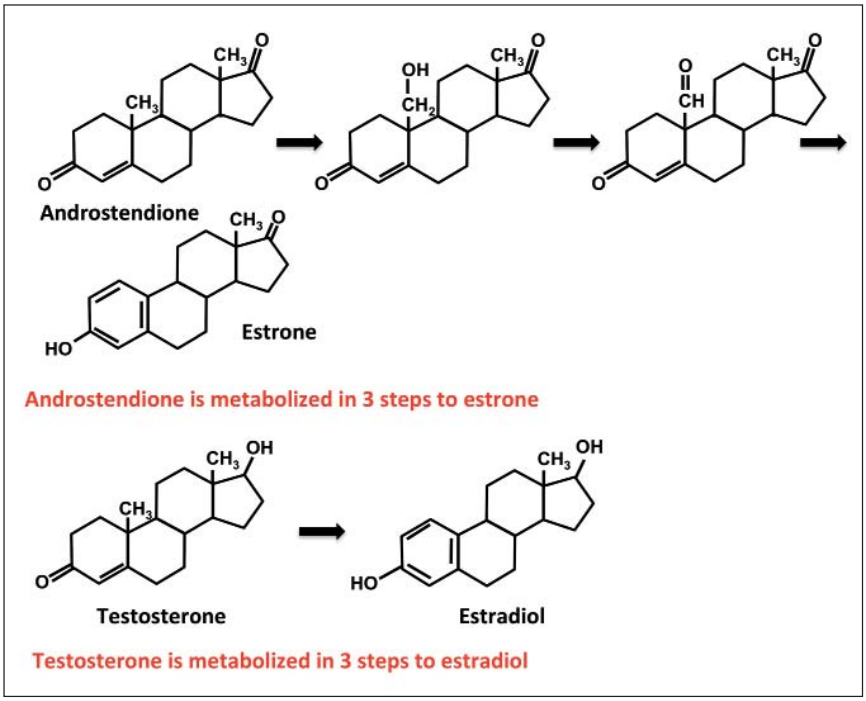

Figure 1. Aromatase: Conversion from testosterone to estradiol. From: Wikipedia, the free encyclopedia. GNU License (http://en.wikipedia.org/wiki/Aromatase).

dren include ovulation induction in reproductive medicine [2] as well as the treatment of uterine fibroids [3] and the treatment of short stature in boys up to 16 years with ISS (idiopathic short stature), lack of growth hormone or constitutional delay of growth and puberty [4]. 2 of 3 Cochrane-Reviews on trials in these indications were begun, but have not been completed [2, 4]. The Cochrane-Review concerning uterine fibroids is confined to a trial with 70 patients, the results of which showed a reduction of fibroid size under AI [3]. This effect may be more pronounced in patients with african origin, as another trial in afro-american women found two-fold higer aromatase mRNA-expression in uterine fibroids [5].

In addition, trials with aromatase inhibitors have been conducted for pubertal gynecomastia, adrenogenital syndrome and premature puberty were conducted. AI have also been used for treatment of male infertility and endometriosis. For all these fields of application there has been no formal approval so far, use of AI in these clinical situations is invariably off-label.

AI decrease E2-serum levels to < 3pmol/l in postmenopausal women (who usually have circulating estradiol levels of 25–30 pmol/l, depending on their amount of body fat). Intracellular estrogen concentrations are decreased, too [6]. Under adjuvant therapy (early breast cancer, without metastases) due to this estrogen deprivation the absolute risk of relapse or recurrence of disease compared with tamoxifene is reduced by 2.7% after 5 years. The 100-month-analysis of the ATAC- trial did not find any effect on the overall survival [7]. In the advanced (metastasized) disease situation, a Cochrane-Review-metaanalysis of 31 trials studying performance of AI in a total of 11.403 postmenopausal patients with advanced breast cancer showed a statistically significant 10% improved survival compared with the other endocrine therapy options tamoxifene, megestrolacetate (MA) and medroxyprogesterone-acetete (MPA) (HR 0.90;95-%-CI: 0.84–0.97). Despite very limited data concerning the differences between the several aromatase inhibitors, letrozol seemed to be more effective than anastrozol [8].

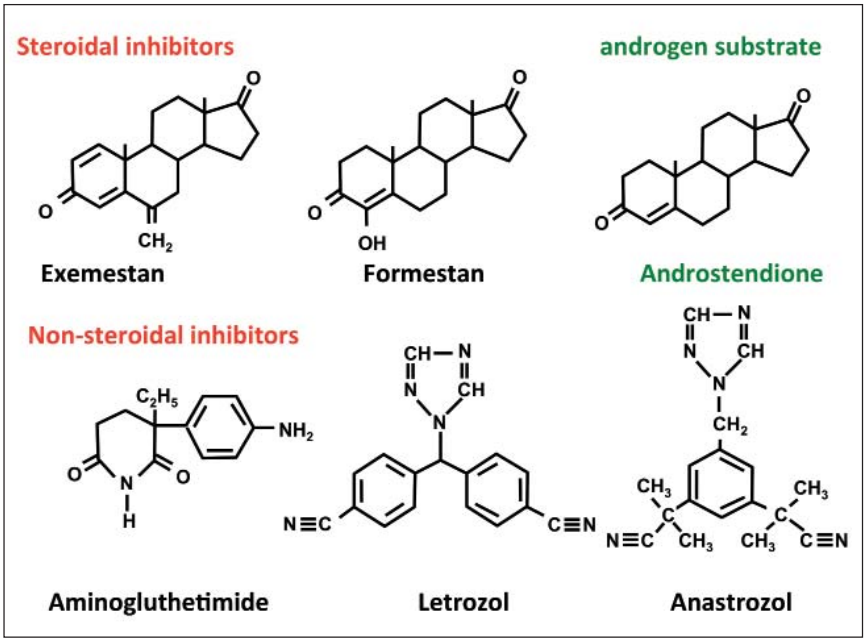

Figure 2. Chemical Structure of AI. (Note: Aminoglutethimid is no longer in clinical use). Translation from: Rabe T (ed.) Seminar in Gynäkologischer Endokrinologie – Band 2. Heidelberg, 2013; 520. Reprint with permission.

AI Application in Premenopause and Reproductive Medicine

13% of all breast cancers occur in women under 45 years, 22% occur in the age group 45–54 years. The average age for menopause is 52 years, the average age at diagnosis for breast cancer patients is around 51 years [9]. Since AI are said to produce a decrease of estrogen production, it could wrongly be supposed that AI-mono-therapy is also a benefit for the patient in pre- and peri-menopause as well as in postmenopause. One publication in reproductive medicine stated a 50% reduction of serum-estradiol concentration under 5 mg Letrozol per day. However, this did not mean reduction of absolute estradiol values to a low level like in postmenopause, but a reduction of extremely high estradiol values (2337 pmol/l) to 1214 pmol/l [10]. A trial that stimulated 47 breast cancer patients and

Table 1. AI: Overview over Compounds. Translation from: Rabe T (ed). Seminar in Gynäkologischer Endokrinologie – Band 2. Heidelberg, 2013; 521. Reprint with permission.

Substance	Pharmacology	Compound and Producer	Formulation	Dosage
Exemestane	Irreversible steroidal AI, gastroenteral resorption, no dose adjustment necessary with hepatic insufficiency or renal failure, max. level after 2 hours, inactive metabolites, daily dose reduces estrogen level by 98%	Aromasin® (Pfizer) and numerous generic medicinal products	1 tablet contains 25 mg Exemestan	1 tablet daily, ingestion preferably after a meal, simultaneous food intake increases bioavailability by 40%
Anastrozole	Highly selctive, nonsteroidal AI; reduces estrogen level in postmenopausal women by > 80%;plasma protein binding 40%, elimination-half-life 40–50 hrs., caution in patients with disorders of renal function.	Arimidex® (AstraZeneca) and numerous generic medicinal products	1 tablet contains 1 mg Anastrozol	1 tablet daily, no interaction between food intake and the amount of resorption
Letrozole	Highly specific nonsteroidal AI; inhibition of estrone and estradiol by up to 78% in postmenopausal women; max. effect after 48–78 hrs. plasma protein binding approx. 60% (55% Albumin); caution with severe disorders of hepatic function: individual risk-benefit-analysis	Femara® (Novartis Pharma) and Numerous generic medicinal products	1 tablet contains 2.5 mg Letrozol	2.5 tablet daily; ingestion before, during or after a meal, simultaneous food intake reduces speed of resorption but not the extent of resorption

56 not carcinoma-diseased women for IVF, used Letrozol and FSH and noted estradiol-levels of 483 under letrozol vs. 1464 pg/ml for conventional stimulating schemes [11]. Therefore, AI (like any other hormonal stimulation) are not recommended for hormone-receptor positive breast cancer [12].

The reason for using AI for women who do not have breast cancer in reproductive medicine is the increased follicular sensitivity towards FSH under AI, whereby during a stimulation therapy for in-vitro fertilization, lower FSH doses are needed and thus costs can be considerably reduced. Moreover, letrozol was applied successfully for ovulatory induction in polycystic ovary syndrome (PCOS) with clomiphen-resistance [13].

Aspects during Perimenopause

During perimenopause, an endogenous hyper stimulation occurs because of the endogenously increased FSH values. This hyper stimulation can persist for weeks, later for months and may recur until early menopause [14]. When an AI-therapy has begun, which further stimulates the follicular sensitivity of the still responsive ovary, even women > 50 years may have strongly increased estradiol values for reccuring periods, even after long phases of amenorrhoea [9]. In contrast to a therapy with a selective receptor modulator (SERM), there is no protection of estrogen responsive tissues by occupation of the estrogen receptors under these circumstances, so that the proliferating effect of follicular estradiol production could potentially stimulate breast cancer residues, too.

Substances (Tab. 1)

Exemestane is a steroidal AI, which inactivates the enzyme by covalent binding on the binding site of the substrate, while anastrozole and letrozole are non-steroidal AI which block the enzyme competetively and reversibly by a binding to the Heme-molecule.

Aminogluthemid, an early AI, which is no longer in clinical use, lead to a hypocortisolism due to unselectively blocking adrenal cortison production. With modern AI, adrenal effects are minimal.

All 4 AI are listed in category S4 by the world anti-doping agency (WADA) as prohibited drugs, since aromatase inhibitors block the conversion of testosterone to estrogens, and thereby may lead to unphysiological androgen concentrations, especially in conjunction with external testosterone supplementation [15].

Dosage

Anastrozol 1 mg p. o. daily, Letrozol 2.5 mg p. o. daily, Exemestan 25 mg p. o. daily

Contraindications

- Known severe allergic reactions to any of the components
- Inducible porphyrias
- Pregnancy and breastfeeding time
- Perimenopause and premenopause

Adverse events

- Common: Climacteric compliants, hot flushes, pain in joints and muscles
- Uncommon: tiredness, drowsiness, increase of the liver enzyme gamma-GT
- Occasionally: depression, adynamia, night mares
- With high doses: ataxia, gastrointestinal complaints, vision disturbances
- Rare: allergic alveolitis, hypothyroidism, leucopenia, agranulocytosis

(See also the section: Side effects and their management)

Drug Elimination and Drug Interactions

- The effect of AI may be diminished by concomitant intake of glucocorticoids, medroxyprogesteronacetat, digitoxin and theophylline.

– Concomitant use of AIs may lead to accelerated elimination of cumarin-derivates and oral diabetics.
– The safety profile of AI use may be impaired if other steroidal hormones are simultaneously applied.

AI in the Treatment of Breast Cancer

Adjuvant Therapy of early Breast Cancer

The magnitude of effect by endocrine therapy is best illustrated by the results of the EBCTCG (Early Breast Cancer Trialists' Collaborative Group) metaanalysis, which showed a reduction of the annual relapse risk of 41% and reduction of mortality risk of 34% for over 10.000 patients with estrogen receptor positive carcinomas who were treated with tamoxifen instead of placebo over 5 years. In total, after 5 years of tamoxifen therapy 9.2% more patients had survived after 15 years of follow-up [16].

In situations where an adjuvant chemotherapy is also indicated, the endocrine therapy should be given sequentially after the cytotoxic therapy, since the simultaneous intake of tamoxifene and a chemotherapy containing antracycline led to a significant reduction of the effectiveness of the chemotherapy (FEC) [17]. In the clinical routine, this sequential chemo-endocrine therapy has been transferred to the use of aromatase inhibitors without having confirmed this concept in clinical trials.

Switch-Concept

This concept entails two years of tamoxifene, followed by a switch to AI for 3–5 years. A metaanalysis comparing the upfront AI-therapy for 5 years with the switch-therapy of tamoxifene to AI after 2–3 years in over 9000 patients found improved disease-free survival for the switch-concept as well as a benefit for mortality of 0.7% after 3 years and of 1.6% after 6 years.

The Intergroup Exemestane Study (IES) examined 4724 postmenopausal women with mainly hormonreceptorpositive early breast cancer with regard to the question whether in the adjuvant situation after 2 or 3 relapse free years under tamoxifene a switch towards the steroidal AI was superior to continuing on tamoxifene-therapy. During ongoing treatment, the benefit was clear (HR 0.60; 95-%-CI: 0.48–0.75), after 8 years (approximately 3 years after the end of adjuvant therapy) over 80% of all patients were alive in both treatment arms, with about 2.4% more patients in the switch (to AI) arm (CI 0.1–4.4). Slightly less than 80% of the patients were disease free at this point; here the absolute difference was 4.5 % in favor of the switch to exemestane group [18].

A clear dominance of the sequential switch-therapy compared with the upfront therapy has not been documented, however this scheme often fits well for younger women with unclear postmenopausal state. These women may profit most from tamoxifene protection of estrogen receptors against endogenous estrogen, followed by AI-therapy once their ovarian estrogen production has subsided. For women with hormone receptor positive breast cancer the absolute reduction of relapse/recurrence after 5 years of adjuvant therapy with AI was 2.7% compared to tamoxifene [9], though this analysis did not make a clear difference between peri- and postmenopausal women.

Extended Use

New data from the ATLAS trial show that 10 years of tamoxifene intake resulted in a small but significant advantage compared with the usual standard of 5 years for disease free – and overall – survival [19].

Due to current data documenting its superiority, the German AGO commission prefers the sequential therapy for up to 10 years with the highest level of Evidence for the sequence tamoxifene followed by AI (LoE, GR A, AGO +++). The sequence AI followed by tamoxifene is preferred in node positive patients, if they are truely postmenopausal at initiation of treatment.

AI treatment for advanced Breast Disease

Due to milder side effects than chemotherapy, in case of metastases an endocrine therapy should be initiated for patients with hormone receptor positive disease. Exceptions are rapid progression of disease in vital organs such as liver or lung, with a high remission pressure or brain metastasis, since chemotherapy can hasten the response to treatment by a few weeks.

AI are one potent therapeutical option amongst others, including tamoxifene, GnRH analogues, the estrogen receptor-antagonist fulvestrant and high dose progestins. Premenopausal women should be given the AI only in combination with a GnRH analogue.

In a Cochrane-Review-metaanalysis of 31 trials studying AI in 11,403 postmenopausal patients with advanced (metastasised) breast cancer, a statistically significant 10% improved survival was seen in comparison with the other endocrine options tamoxifene, megestrolacetate (MA) and medroxyprogesteronacetet e(MPA) (HR 0.90, 95-%-CI: 0.84–0.97). Limited data concerning the differences between the various aromatase inhibitors named letrozol to be slightly more advantageous than anastrozol [8].

For breast cancer expressing Her2 neu in postmenopausal patients, the combination therapy of aromatase inhibitors and trastuzumab or lapatinib is effective and approved [20–22].

For Her2 neu negative, hormone receptor positive disease a targeted combination-therapy with exemestane and the m-TOR inhibitor everolimus is possible [23] after progression of disease under a nonsteroidal AI (letrozol, anastrozol).

Side Effects and their Management

Vaginal Dryness

Vaginal dryness is a common problem in breast cancer patients under AI-therapy. In order to alleviate and prevent painful recurring vaginal and urinary tract infection – often necessitating antibiotics –, local application of lactobacillus or lactic acid, as well as estradiol-containing vaginal treatments are common. After initial 14 days of daily application in the evenings, maintenance therapy is continued twice a week. Systemic effects are minimal under this therapy, yet occasionally patients report breast tenderness or pain in the lower abdomen under therapy with estradiol. A study found merely a transient increase of serum-estradiol levels. Low dosed estradiol-therapy is regarded as a safe and effective therapy of atrophic colpitis under nonsteroidal AI [24].

Due to the very low intracellular conversion of estradiol (E3) to the systemically

more potent estradiol (E2) the local therapy is considered a low-hazard option in the eyes of many experts, despite a lack of guaranteed harmlessness proven by large trials. Vaginal estradiol should be avoided, a small trial on seven patients under AI detected increases of E2 values under application of local E2 (Kendall 2006) (25). When estradiol directly acts on mamma-carcinoma cell-lines in vitro, estrogenic effects of estradiol on gen-expression and growth [26] were observed.

Hot Flushes and Night Sweats

Under aromatase inhibitors hot flushes occur as often as under tamoxifene and less than in comparison with MPA (OR 0.20, 95-%-CI: 0.06–0.73), but more often than under therapy with MA (OR 1.73, 95-%-CI: 1.40–2.14) [8]. Non-estrogenic substances effective for treating hot flushes are Cimicifuga racemosa, St. John's wort, SSRIs, Gabapentin, Tocopherol 800IE/d (Vitamin E), sage extracts, as well as regular physical exercise, relaxation techniques, and the avoidance of coffein, alcohol or spicy food.

For phytoestrogens (soy products etc) a guaranteed harmlessness for postmenopausal women under AI can not be granted, as the main ingredients genistein and daidzein bind to the estrogen receptor, and may be enriched in some more refined soy preparations. Premenopausal women may profit from the binding of phytoestrogens to estrogen receptors, thereby possibly preventing the binding of more potent endogenous estradiol, but no larger trials have been conducted on this question.

Bone Pain, Arthralgia and Myalgia

In the adjuvant therapy situation, a higher rate of bone and joint pain was documented under AI than under tamoxifene [8]. Treatment options include mainly NSAIDs, positive effects on bone pain under bisphosphonates are also described.

Gastrointestinal Pain, Nausea and Emesis, Diarrhoea

While nausea and emesis were equally common under tamoxifene and aromatase inhibitors, diarrhoea occurred more often under AI-therapy (OR 1.64). There were no statistically significant differences to fulvestrant, while compared with megestrolacetate there were significantly less patients with gastrointestinal complaints (under AI: OR 1.77 for nausea, OR 2.03 for emesis, OR 1.48 for diarrhea) [8].

Thromboembolic Events

Data from six trials with 2937 women showed statistically significant less thromboembolic events under AI in comparison with tamoxifene (OR 0.48, 95-%-CI: 0.27–0.85), but not in comparsion with MA or fulvestrant (estrogen-receptor-antagonist) [8].

Eczema and Skin Rashes

15 studies with 4598 women reported data concerning skin eczema; here the odds ratios for eczema under aromatase inhibitors were strongly increased (OR 33.6 compared with tamoxifene and OR 36.8 in comparison with MPA). Treatment is usual with topical substances in most cases [8].

Fracture Prophylaxis

Fracture rates of around 3% annually are described under aromatase inhibiting treatment versus 2% under tamoxifene [8]. A fracture-risk of 3% – i.e. a 10 year fracture risk of 30% – corresponds to the level of risk at which a specific osteoporosis therapy is indicated according to the guidelines of the German osteologic societies (DVO guideline: http://www.dv-osteologie.org/dvo_leitlinien/osteoporose-leitlinie-2014). Therefore, before the initiation of AI-therapy, a bone density measurement and in the given case of low bone density ≤ 2.0 T-Score either fracture prophylaxis with bisphosphonates or (in situations with low risk of breast cancer recurrence) alternative adjuvant treatment with tamoxifene should be thought of. In cases of osteoporosis, ibandronate every 3 months i. v., zoledronate (Aclasta 5 mg once yearly i.v.) and denosumab (Prolia® 60 mg once every 6 months s. c.) are the approved substances. Zoledronate is also in use in the 4 mg dose (Zometa®) every 6 months for prevention of bone metastases, so far without published evidence of effect and without approval (the ongoing D-CARE trial investigating Denosumab in the adjuvant therapy for breast cancer is not finished yet). In advanced disease, Denosumab 120 mg monthly (Xgeva®) was slightly superior to zoledronat (4 mg Zometa® monthly) in treating manifest metastases to the bones.

See also the section on cancer-therapy induced bone disease (CTIBD) below.

Interdisciplinary Aspects of the Choice of Therapy

Two non-oncologic criteria play a relevant role for or against an AI-therapy:

1.) Unclear menopausal status

For aromatase inhibiting therapy it is of importance whether a patient is peri- or postmenopausal, since for estrogen-depriving therapy of breast cancer AI are exclusively reserved for the postmenopause, because aromatase inhibitors lead to a FSH increase und this can lead to an increase of the ovarian estrogen production in not yet fully postmenopausal women. In women who had mistakenly been classified as postmenopausal merely on grounds of their bleeding history (e. g. amenorrhoea after chemotherapy), estradiol levels of up to 500 and 600 pg/ml were measured under a treatment thought to abolish the effect of estrogens on residual tumor cells [27].

Due to safety considerations in such situations, tamoxifene can be given in dubious cases. It has an effect in premenopause as well as in perimenopause. Otherwise, the ovarian response to the aromatase-inhibitor effected increase of FSH can be eliminated by GnRH-analogues (ABCSG 12-trial, TEXT und SOFT-trials, compare [28]). As tamoxifene leads to a discordance between biochemical and clinical menopause, in dubious cases women with an age of 60 or older can safely be assumed to be postmenopausal [9].

2.) Patients with a history of manifest osteoporosis or very low bone density and/or strong risk factors for fracture

It has to be taken into consideration, that there is a clear dependence between the frequency of fractures and age, which is stronger than the correspondence between bone density and fracture risk.

Oncologic trials published so far have not considered the baseline risk of fracture or falling for the particular patient. This however seems to be a factor which should be considered in the decision-making for adjuvant therapy. Absolute mortality rate is at its highest in the 5 years after a hip fracture and can exceed the risk of dying from breast cancer in elderly women. The aim of therapy is not

only relapse free survival but also that the breast cancer-therapy does not do more harm than it is of use (quality of life in longer survival). This will lead to individual therapy decisions when considering interdisciplinary aspects (beyond breast cancer). In fact, very slim and underweight women with a low thrombosis risk and a high osteoporosis risk could possibly benefit more from other endocrine therapies than from aromatase inhibitors for their overall survival, but there are no trials yet on this patient-centered approach to treatment.

Pathophysiology and Treatment of Cancer-Therapy-Induced Bone Disease (CTIBD)

The largest loss of bone density results in the first 24 months after the beginning of AI-therapy [29], and the rate of loss is highest for those patients who previously had a relatively high bone density, i. e. premonopausal and early perimenopausal breast cancer patients, those who had taken hormone therapy up to the diagnosis, but also after tamoxifene-therapy. Bisphosphonates reduce the vertebral fracture risk of patients with osteoporosis and can eliminate aromatase inhibitor-associated bone loss. Data concerning fracture reduction, especially after breast cancer are weak so far [30].

Though the negative influence of aromatase inhibitors on bone density is known, an osteoporosis prophylaxis is not initiated frequently enough. Another hindering factor is that although the guidelines of several professional associations recommend a bone density measurement before beginning an AI-therapy, these measurements are not offered under health insurance coverage in many institutions.

A consensus of the 2007 St. Gallen conference was that a bone density measurement at the beginning of an AI-therapy is recommended, and that bisphosphonates should be given if necessary.

According to the American Society of Oncology (ASCO) guidelines, a bone density measurement and possibly bisphosphonates are recommended at the beginning of AI-therapy, especially for women with breast cancer in early postmenopause for whom AI are indicated, because these depict a high risk group for osteoporosis [31], such as the 25% of early postmenopausal women who display particularly accelerated bone loss. If the initial T-Score is higher than –2,5, annual control of bone density under AI is recommended, and subsequent initiation of therapy is recommended with a T-Score of ≤ –2,0 to –2,5 [32].

The guidelines 2010 of the working commitee Gynaecologic oncology (AGO) also list bisphosphonates for the prevention and therapy of a tumor-therapy induced osteoporosis. This committee also recommends bisphosphonates for the prevention of bone metastases. However, a Cochrane-Review concerning bisphosphonates and other bone-relevant drugs found insufficient evidence of a benefit of adjuvant bisphosphonat-therapy in breast cancer patients up to 2011 [33].

Two additional components contribute to the loss of bone density: chemotherapy and corticosteroids have a direct and early effect on bone metabolism on the one hand, on the other hand especially premenopausal and perimenopausal patients who suffer from indirect effects through chemotherapy induced ovarian toxicity and resulting estrogen deprivation experience accelerated bone loss. Both mechanisms mostly affect trabecular bone, which reacts quickly to hormonal changes and which is predominant in the spine. This is the reason for an increased long-term risk of fractures of the vertebrae. As in all patients receiving bisphosphonates or denosumab, a sufficient supply of vitamin D and calcium as baseline-therapy is a key requirement for sufficient bone effectiveness of any specific bone treatment. As both classes of substances (bisphosphonates especially after being injected) lower the level of serum calcium for approximately 4 weeks it is important to assure sufficient calcium intake during this period of time, regular testing of serum calcium and – under bisphosphonate-therapy – of renal function tests (contraindication for some bisphosphonates, if GFR < 60) are recommended.

To improve therapy, oncologists and osteologists should cooperate more intensively [29], which often fails in practice due to not yet fully developed cooperation structures.

Future Developments

The role of aromatase inhibitors in the adjuvant therapy of premenopausal breast cancer patients with ovarian suppression was already tested in the ABCSG 12 trial but was tested on further more than 4690 women since 2003 in 2 longitudinal trials: the tamoxifene and exemestane Trial (TEXT) trial investigated exemestane versus tamoxifene in combination with ovarian suppression, the suppression of ovarian function trial (SOFT) examined both in comparison with a third trial arm with tamoxifen alone. The first combined analysis of both trials, pooling 4690 women after a median follow-up of 68 months, reported disease-free survival at 5 years to be 91.1% in the exemestane-ovarian suppression group and 87.3% in the tamoxifene-ovarian suppression group (hazard ratio for disease recurrence, second invasive cancer, or death, 0.72; 95-%-CI, 0.60–0.85; p < 0.001). The rate of freedom from breast cancer at 5 years was 92.8% in the exemestane-ovarian suppression group, as compared with 88.8% in the tamoxifene-ovarian suppression group (hazard ratio for recurrence, 0.66; 95-%-CI: 0.55–0.80; p < 0.001). With 194 deaths (4.1% of the patients), overall survival did not differ significantly between the two groups (hazard ratio for death in the exemestane-ovarian suppression group, 1.14; 95-%-CI: 0.86–1.51; p = 0.37). Selected adverse events of grade 3 or 4 were reported for around 30% of the patients for both combinations [28]. The combination of AI with the anti-estrogen fulvestrant was not more effective than any of both substances on its own (SoFEA Investigators) [34]. Further ongoing trials investigate the combination of aromatase inhibitors with neutralising antibodies against IGF-1 or its receptor, i. e. ganitumab [35], metformin and inhibitors of P13k and/or Akt. Some of these targeted therapy approaches try to overcome endocrine therapy resistances [36], which is also the aim of trials investigating reverse switch concepts, like switching from AI-therapies to toremifen, a SERM [37].

Summary

From studies and meta-analyses of the last 25 years on endocrine therapy of breast cancer, we may reason:

1.) Standard today is AI-therapy for 5 years. For tamoxifene, two studies are published (aTTOM und ATLAS) which argue for treatment over 10 years. For

aromatase inhibitors such data do not yet exist.

2.) The choice of therapy (tamoxifene, aromatase inhibitors or their sequence) depends considerably on risk factors for side effects of the particular class of endocrine treatment (e. g. thrombosis with SERMs, osteoporosis with AI) as well as on the tolerance of side effects of the substance by the individual patient. Although the first choice treatment of a hormone receptor positive breast cancer is aromatase inhibition, an individual decision – possibly including phase of the menopausal transition - may alter this choice to tamoxifene or a sequence therapy (switch).

3.) AI upfront are preferred for clearly postmenopausal patients with a higher oncologic risk and for patients with a lobular carcinoma. Changing from one substance to the other is better than stopping therapy altogether.

Endocrine therapy is essential in the treatment of patients with a hormone-sensitive breast cancer. The decision for an AI has to comply with the individual risk of the patient, her state of menopause, her co-morbidities and the tolerability of the particular substance. Duration of treatment should be 5–10 years, depending on the criteria mentioned above.

Conflict of Interest

The authors declare no conflict of interest.

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