Breast Care

Review Article · Übersichtsarbeit

Breast Care 2009;4:155–161
DOI: 10.1159/000227829

Published online: June 23, 2009

Is Endocrine Therapy Really Pleasant? Considerations about the Long-Term Use of Antihormonal Therapy and Its Benefit/Side Effect Ratio

Peter Blaha Ruth Exner Andrea Dal Borgo Sinda Bigenzahn Peter Panhofer Otto Riedl Sebastian Schoppmann Thomas Bachleitner-Hofmann Emanuel Sporn Ursula Pluschnig Florian Fitzal Guenther Steger Raimund Jakesz Peter Dubsky Michael Gnant

Department of Surgery, Medical University of Vienna, Austria

Key Words

Endocrine therapy · Breast cancer · Tamoxifen · Aromatase inhibitors · Anastrozole · Letrozole · Exemestane · Side effects · Tolerability · Safety

Summary

Endocrine therapy has become a key part in the adjuvant treatment of hormone responsive breast cancer. The positive effect on relapse risk reduction is well defined, but therapy is not free from bothersome side effects for which estrogen deprivation accounts to a great extent. Since endocrine therapy is usually prescribed for 5 years or longer to optimally display its protective effect, and because physical strain is missing, good tolerability and safety properties are important, particularly in low-risk patients. While tamoxifen has been the standard adjuvant endocrine treatment with well documented efficiency, it is increasingly replaced by third generation aromatase inhibitors due to their better effectiveness and tolerability. Because tamoxifen holds a risk for life-threatening adverse events such as endometrial cancer, pulmonary embolism, and stroke, its recommended duration of therapy is limited to 5 years, also because extension beyond that time did not produce a measurable advantage. While some side effects are present both with tamoxifen and aromatase inhibitors, differences in side effect profiles are well established. Although side effects of aromatase inhibitor-related therapy usually are mild and common to symptoms of menopause, misconception of the symptoms and their mechanism of action, as well as lack of knowledge about how to handle them, can easily lead to dangerous discontinuation of therapy.

Schlüsselwörter

Endokrine Therapie · Nebenwirkungen · Tamoxifen · Aromataseinhibitoren · Anastrozol · Letrozol · Exemestan · Verträglichkeit · Sicherheit

Zusammenfassung

Endokriner Therapie kommt mittlerweile eine Schlüsselrolle bei der adjuvanten Therapie von Patientinnen mit hormonrezeptorpositivem Mammakarzinom zu. Der positive Effekt auf die Reduktion des Rückfallrisikos ist gut dokumentiert, allerdings ist die Therapie nicht frei von Nebenwirkungen, welche zum Großteil auf den Entzug der Östrogenwirkung zurückzuführen sind. Da endokrine Therapie üblicherweise für 5 Jahre oder länger verschrieben wird, um die positiven Effekte auszuspielen, und physischer Leidensdruck in dieser Zeit nicht vorhanden ist, kommt der optimalen Verträglichkeit und Sicherheit der Therapie eine besondere Bedeutung zu, speziell bei Patientinnen mit niedrigem Risiko. Während Tamoxifen die Standardtherapie mit gut dokumentierter Wirksamkeit war, wird es wegen besserer Verträglichkeit und Wirksamkeit immer mehr von Aromataseinhibitoren (AI) der dritten Generation abgelöst. Die Therapie mit Tamoxifen ist auf 5 Jahre limitiert, da das Risiko für lebensbedrohliche Nebenwirkungen wie Endometriumkarzinom, Pulmonalembolie und Schlaganfall erhöht wird und kein zusätzlicher Nutzen für eine verlängerte Therapie nachgewiesen werden konnte. Während manche Nebenwirkungen unter Tamoxifen wie unter AI auftreten, bestehen auch typische Unterschiede zwischen den beiden Substanzgruppen. Obwohl AI üblicherweise nur mit milden Nebenwirkungen, ähnlich menopausalen Beschwerden, verbunden sind, können Missverständnisse bezüglich der Wirkungsweise, der Symptome und dem richtigen Management der Beschwerden zu einem gefährlichen vorzeitigen Therapieabbruch führen.

KARGER

Fax +49 761 4 52 07 14
Information@Karger.de
www.karger.com

Accessible online at:
www.karger.com/brc

Prof. Dr. med. Michael Gnant
Abteilung für Allgemeinchirurgie
Universitätsklinik für Chirurgie MUW
Währinger Guertel 18–20, 1090 Wien, Austria
Tel. +43 1 40 400-5646, Fax -6807
michael.gnant@meduniwien.ac.at

Introduction

The introduction of endocrine adjuvant therapy effected a significant risk reduction for relapse and increased life expectancy for millions of women with hormone receptor-positive (HR+) breast cancer. Endocrine therapy is sufficiently nontoxic to be administered long-term, with standard treatment duration of 5 years and more after concluded local therapy for breast cancer. Any regular and long-term medication calls for excellent safety and tolerability to ensure compliance and effectiveness, especially when physical strain and the subjective experience of disease are missing, and the patient's involvement and consciousness about the persistent risk of breast cancer is necessary but often unwanted by her.

Tamoxifen was the most successful agent being introduced for endocrine therapy in women with and after HR+ breast cancer. By now, safety, effectiveness, and tolerability are well documented after more than 25 years of its clinical use. Although the protective effect against relapse of HR+ breast cancer is undisputed, the critical risk-to-benefit ratio does not allow treatment duration more than 5 years, especially in node-negative patients [1, 2]. The drug is generally well tolerated but infrequently associated with life-threatening events such as endometrial cancer, thromboembolic events, and stroke.

As the standard of care, tamoxifen now has been replaced by third generation aromatase inhibitors (AIs) in the adjuvant setting due to better efficacy and tolerability, as recommended by many national and international guidelines. While AI therapy can elicit a bothersome side effect, namely arthralgia, the life-threatening adverse events sometimes seen under tamoxifen are in general missing. Other AI side effects include decrease of bone mineral density, treatment-induced osteoporosis, and subsequent increase of fracture risk. These are of concern but not directly felt by patients. Serious adverse events in general occur less frequently, and discontinuation rates are lower under AI therapy than under tamoxifen [3, 4]. The optimal treatment duration with AIs is still not defined but the better tolerability profile compared to tamoxifen at least in principle allows for an extension to more than 5 years.

While adjuvant endocrine treatment improves the outcome after HR+ breast cancer for millions of women with an arguable benefit/side effect ratio, the downside of being treated with agents like tamoxifen and AIs, mostly resulting from estrogen deprivation, should not be ignored. Since it is important to understand the mechanism of action of side effects for successful supportive therapy without treatment discontinuation, patients benefit from being informed about all aspects of the therapy they are willing to subject themselves to for many years. We truly believe that it is also extremely important for the caring physician both to accumulate knowledge and to openly communicate with patients about tolerability issues since he or she will then contribute to treatment adherence.

The raised question whether endocrine therapy is a pleasant one is a matter of interest for patients and physicians alike. 'Pleasant' may be a suboptimal term since it may be asking to much of an anti-cancer treatment to even have positive effects on patient's quality of life. Probably, 'acceptable' would be good enough. It is certain that the therapy is beneficial in terms of risk reduction and improvement of life expectancy, but we will try to fathom the benefit/side effect ratio of modern adjuvant endocrine treatment from different angles in this review.

Side Effects

AIs and tamoxifen share some of their side effects, mainly due to the deprivation of estrogen, while on the other hand there are characteristic side effects for AIs or tamoxifen alone. Tamoxifen, as a selective estrogen receptor modulator (SERM), competitively blocks estrogens receptors in the peripheral tissue while AIs reduce estrogen output and synthesis by blocking the enzyme crucial for conversion of androgens to estrogens in peripheral tissues: aromatase. Apart from estrogen deprivation-associated side effects such as mood swings, hot flushes, and hair loss, adverse events associated with tamoxifen include an increased risk of endometrial cancer due to an agonistic effect of the substance on the endometrial tissue and thromboembolic complications such as pulmonary embolism, deep vein thrombosis, or stroke [5]. AIs on the other hand are not connected with life-threatening complications of this kind but can cause perturbing side effects like arthralgia, myalgia, or osteoporosis. Their described negative impact on blood lipid metabolism was never clearly established. From the patient's point of view, the most bothersome endocrinological side effects are hot flashes, weight gain, insomnia, and joint symptoms, side effects which concern tamoxifen and AIs alike [6].

Elevation of Endometrial Cancer Risk

While the protective effect of tamoxifen against relapse of HR+ breast cancer results from an antagonistic effect on breast tissue, it acts as an agonist on hormone receptors in the endometrium, and thus can result in unwanted gynecological symptoms such as vaginal bleeding, vaginal discharge, endometrial proliferation, and ultimately increased incidence of endometrial cancer, especially compared to AIs [7–9]. A meta-analysis of 32 trials including 52,929 patients came to the clear conclusion that tamoxifen intake is associated with a significant elevation of endometrial cancer risk (relative risk 2.7) and gastrointestinal cancer risk (relative risk 1.31) [10], which is one the main reasons why tamoxifen therapy duration is limited to 5 years.

Another reason for the limitation of tamoxifen therapy to 5 years is the fact that therapy beyond that time frame did not deliver any further measurable advantage. 1,152 women with HR+ and node-negative breast cancer participated in

the randomized NSABP B-14 trial after completion of 5 years tamoxifen therapy, receiving either tamoxifen or placebo for an additional 5 years. 7 years after randomization, disease-free survival (DFS) was significantly better for the placebo group compared to tamoxifen (82 vs. 78%), overall survival (OS) was (not significantly) better for women who had received tamoxifen for only 5 years compared to continued therapy of 7 years [1]. The apparent lack of benefit for continuing tamoxifen therapy beyond 5 years led to the termination of the trial. Despite some positive signals from the ongoing ATLAS and ATTOM trials, in view of the potentially serious adverse events, especially endometrial cancer, thromboembolic complications, and stroke, prescription of tamoxifen for more than 5 years is generally not recommended.

Thromboembolic Complications

The ATAC trial, a retrospective analysis comparing the effectiveness of anastrozole vs. tamoxifen in the treatment of early HR+ breast cancer in 5,216 women, evidenced that tamoxifen therapy leads to significant elevation of venous thromboembolic complications (3 vs. 5%, n = 6,186) after a median follow up of 68 months [4] in comparison to anastrozole. The large meta-analysis by Braithwaite et al. [10] backed these data by showing significant increases in deep vein thrombosis (relative risk 1.87), pulmonary embolism (relative risk 1.88), and stroke (relative risk 1.49) under tamoxifen therapy. Similarly, patients receiving letrozole experienced significantly less thromboembolic events compared to patients receiving tamoxifen (2 vs. 3.8%), as evaluated in the BIG 1-98 trial [8]. In the combined analysis of the Austrian Breast And Colorectal Cancer Study Group (ABCSG) Trial 8 and ARNO 95 trial, 3,224 postmenopausal women with HR+ early breast cancer and after completion of 2 years of adjuvant tamoxifen therapy were assigned to further tamoxifen or switched to anastrozole. Significantly fewer thromboembolic events were found in the anastrozole group compared to tamoxifen [11]. The Intergroup Exemestane Study (IES) reported similar results; after switching from tamoxifen to exemestane, significantly less thromboembolic events occurred in women under exemestane therapy (1.2 vs. 2.3%) compared to women who continued tamoxifen intake beyond 2–3 years [9].

Osteoporosis and Bone Fractures

The balance between bone formation and resorption depends on the activity of osteoblasts and osteoclasts. Some of the key modulators are the levels of estrogen and parathyroid hormone, to a lesser degree also of testosterone. Due to the decrease of estrogen after menopause, bone resorption outweighs formation resulting in physiological decrease in bone mineral density (BMD), osteoporosis, and increased fracture risk. While in principle postmenopausal breast cancer patients are more susceptible to low BMD than other women of the same age (which seems to be largely explained by lower hormone replacement therapy (HRT) usage [12]), the condition aggravates with adjuvant therapy with chemotherapeutics or hormonal therapy, which can decrease BMD and increase the risk for osteoporosis [13].

Tamoxifen repeatedly demonstrated a beneficial influence on bone metabolism, at least in postmenopausal women. In a study evaluating 44 postmenopausal patients after early breast cancer, tamoxifen seemed to display an estrogen-like effect on BMD with a minimal (non-significant) increase in the lumbar spine and femoral neck after 12 months of treatment [14]. Prior to this study, 25 postmenopausal women after early breast cancer were evaluated in a similar setting, where tamoxifen significantly increased BMD in the lumbar spine compared to a control group without tamoxifen, and stabilized BMD in the forearms [15]. A recent Canadian population-based case-control study compared characteristics of 11,096 patients with osteoporotic fractures with 33,209 matched controls. Results showed that current use of tamoxifen led to a significantly lower overall osteoporotic fracture risk [16].

Raloxifene is another SERM, which acts as an estrogen agonist on bone metabolism and has been approved for prevention and treatment of postmenopausal osteoporosis. A 2-year phase II study including 129 postmenopausal patients with osteoporosis or low BMD showed that raloxifene significantly increases BMD in the lumbar spine, femoral neck, trochanter, and total hip, while lowering serum levels of triglycerides and cholesterol [17]. Apart from the protective effect on bones, raloxifene has been demonstrated to reduce breast cancer risk according to its function as a SERM. The Multiple Outcomes Of Raloxifene Evaluation (MORE), an osteoporosis treatment study conducted in postmenopausal osteoporotic women with normal to low risk for breast cancer, revealed that raloxifene led to a risk reduction for HR+ breast cancer by 84%. The substance was well tolerated, but thromboembolic events were reported more often for raloxifene-treated patients than with placebo [18]. Other adverse events included higher incidence of flu syndrome, hot flashes, leg cramps, endometrial cavity fluid, and peripheral edema in comparison to placebo. These very promising results led to the initiation of the Continued Outcomes Relevant to Evista (CORE) study, which investigated the long-term efficacy of raloxifene in reducing the incidence of invasive breast cancer in patients who were previously treated with the substance in the MORE study. During the 4 years of the CORE trial, incidence of HR+ breast cancer was reduced by 66% compared to placebo intake [19]; during the 8 years of MORE and CORE together, risk was decreased by 76% with no significant difference in adverse events. In contrast, an incidence elevation by 49% for fatal stroke and 44% more venous thromboembolic events was seen in another trial which evaluated the possible risk reduction for coronary heart disease in raloxifene-treat-

ed women, which at the end apparently was not existent any longer [20]. Ultimately, these somewhat conflicting data led to the conduction of the STAR trial, comparing the preventive use of raloxifene with tamoxifen in reducing the risk of invasive breast cancer in healthy post-menopausal women at high risk. It became evident that raloxifene and tamoxifen are equal at reducing the risk for invasive breast cancer [21]. Although fewer cataracts, thromboembolic events and hysterectomies were observed among raloxifene-treated women, the incidence of non-invasive breast cancer was increased in this cohort compared with tamoxifen-treated women. Interestingly, although women receiving raloxifene had significantly less uterine hyperplasia, there was no statistical difference concerning uterine cancer. Likewise, the risk for other cancers, ischemic heart disease, and stroke were equal for both drugs.

AIs can lead to bone loss and increased fracture risk due to inhibition of estrogen synthesis. The question if the 3 clinically used AIs differ in terms of their effect on bone metabolism was addressed in an open phase I study including 90 postmenopausal women who received anastrozole, exemestane, or letrozole for 24 weeks. All 3 AIs increased bone resorption markers in a similar way, but did not lead to an increase in bone turnover markers [22]. Similar results were obtained in an analysis of bone resorption markers from 74 women who received anastrozole, exemestane, letrozole, or placebo. Exemestane though, seemed to increase the bone formation marker PINP, maybe due to its androgenic structure [23]. 1,354 patients under aromatase therapy after breast cancer were compared to 11,014 controls without AIs in a retrospective large cohort study which found a significantly higher incidence of bone fractures in the cohort receiving AIs with a relative risk of 1.4 [24].

In large clinical trials evaluating AIs in comparison to tamoxifen, the increased risk for bone loss, fractures, and osteoporosis was evident for anastrozole, letrozole, and exemestane alike. In the ATAC trial, the significantly increased incidence of clinical fractures in comparison to patients receiving tamoxifen (2.93 vs. 1.9%) was proven alongside with significantly better DFS [25]. After completion of the therapy though, this negative effect disappeared. Follow-up results from the BIG 1-98 trial after median 51 months, which compared the effectiveness of letrozole on 2,463 women with early HR+ breast cancer to 2,459 women receiving tamoxifen, evidenced a significantly higher risk for fractures, arthralgia, and elevation of blood lipids under exemestane [8]. These data were supported by findings from the IES; a higher risk for osteoporosis and fractures affected women who were switched to exemestane after 2–3 years of endocrine treatment with tamoxifen [9].

Joint and Musculoskeletal Symptoms

Arthralgia as a therapy side effect has been observed significantly more often under therapy with AIs. The exact underlying mechanism for AI-related joint problems are still unclear, however, it is accompanied by a swelling in tendons of small joints due to increased local fluid retention, which can be visualized by magnetic resonance imaging (MRI). Estrogen deficiency has been recognized as a key factor in the risk increase for arthritis and arthralgia [26]. Significantly higher incidences of arthralgia under AI therapy compared to tamoxifen were reported from the ATAC trial, BIG 1-98 trial, and IES, as well as from the NSABP B-33 which compared exemestane to placebo, with a likelihood of underreporting in all of these trials. The ATAC trial showed that 35.6% of AI-treated patients had to deal with arthralgia compared to 29.4% receiving tamoxifen [7]. Apart from treatment with anastrozole, major risk factors for development of joint symptoms included previous HRT, HR positivity, and obesity [27]. The same issue applies to letrozole, in the BIG 1-98 trial; significantly more patients reported arthralgia than patients with tamoxifen therapy (20 vs. 13.5%) [8]. Nevertheless, reported withdrawal rates due to arthralgia were very low in both groups. Since joint problems are a very bothersome experience, an effective management of this problem helps to avoid discontinuation of the medication. This means a rapid and decisive intervention mainly aiming at pain reduction, e.g. using non-steroidal anti-inflammatory drugs (NSAIDs) at an effective dose. Arthralgia is considered to be the most important cause of non-compliance, and effective communication and intervention is desirable.

Blood Lipid Metabolism

Elevation of serum lipids and weight gain are associated with increased risk of diabetes and coronary heart disease [28], a condition which may physiologically aggravate after age 50 and menopause [29, 30]. While tamoxifen was reported to have a favorable effect on blood lipid metabolism, AIs in contrast do not seem to have such an effect. Tamoxifen reduces total cholesterol and low density lipoprotein (LDL) cholesterol [31], and significantly reduced deaths due to myocardial infarction, according to a meta-analysis of randomized controlled trials [10]. On the other hand, treatment can be associated with an elevation of triglycerides [32] and is complicated by higher incidence of thromboembolic events with a relative risk of 1.9 as seen in a meta-analysis of prevention trials [33].

Anastrozole is associated with a significant elevation of cholesterol and a non-significant higher incidence of ischemic cardiovascular events in comparison to tamoxifen according to results from the ATAC trial [4], but in comparison to placebo, AIs do not result in hypercholesterolemia [41]. Since the risk for cardiovascular events under AI therapy widely accords to age-matched controls without breast cancer [42], clinical management under AI therapy should include regular monitoring of blood lipids and management of preexisting hypercholesterolemia.

Side Effects and Extended Adjuvant Therapy

Since breast cancer recurrence continues to be a threat for women after completion of adjuvant endocrine therapy, extension of therapy beyond the time frame of 5 years attracts attention. Because AIs have a different mechanism of action than tamoxifen, they serve as promising candidates for postmenopausal patients seeking to extend their endocrine treatment. The National Cancer Institute of Canada Cooperative Trials Group MA.17 trial addressed this issue by administering letrozole to postmenopausal women after completion of a 5-year tamoxifen therapy due to the promising results of letrozole in women with progressive disease on previous tamoxifen. The study was unblinded after a median of 2.4 patient years because of the substantial benefits (significantly better DFS and OS in node-positive patients) of extended letrozole therapy, and all patients were offered this option. With the clinical benefit and the OS advantage also seen in women who crossed over from placebo, letrozole clearly can be considered for extension of endocrine therapy after 5 years of tamoxifen [34]. The clear benefit of therapy extension with anastrozole was shown by the ABCSG Trial 6a including 856 patients after completion of 5 years tamoxifen therapy, randomizing patients to a further 3 years of anastrozole therapy or no treatment. At 62.3 months median follow-up, anastrozole therapy led to a significant risk reduction for locoregional recurrence, contralateral breast cancer, and distant metastases [35]. The extension of therapy with exemestane was evaluated in a similar setting by the NSABP-B33 study on 1,598 women who were randomly assigned to exemestane or placebo after completion of 5 years tamoxifen. After a median follow-up of 30 months, exemestane had significantly improved relapse-free survival and showed a trend to improve DFS. Consecutively, these results led to premature closure of the study and substantial cross-over [36]. AIs in these trials were generally well tolerated and were consistent with side effects known from upfront AI therapy.

Adherence Rates

Serious and harmless side effects can lead to discontinuation of the therapy alike. Although discontinuation rates due to side effects seem to be low within the scope of clinical trials, Lin and Winer [37] state that these patients may not be representative for the breast cancer population as a whole. Drops in adherence rates have been described for anastrozole with mean adherence rates of 82–86% after 12 months, decreasing to 62–79% after 3 years [38]. For tamoxifen, drops to 50% overall adherence rate after 4 years have been described [39]. Coombes et al. [9] argued that sequential therapy with tamoxifen and exemestane would reduce side effects (and improve efficacy) compared to therapy with one agent alone, and assigned 4,724 women after 2–3 years tamoxifen to either exemestane or tamoxifen for the remainder of 5 years. The data from this IES project support the rationale of switching to an AI after 2–3 disease-free years on adjuvant tamoxifen therapy. Serious side effects were described to be rare, and some might be attributable to withdrawal from tamoxifen [9]. Switching from tamoxifen to an AI (anastrozole) led to a benefit for patients in another sequential therapy setting: the combined results from the ABCSG Trial 8 and ARNO 95 showed that patients who switched to anastrozole not only gained from a recurrence risk reduction but also had significantly fewer thromboses and a trend towards fewer emboli and endometrial cancer compared to patients who stayed on tamoxifen [11].

Discussion

AI-based endocrine therapy is generally well tolerated, with anastrozole, letrozole, and exemestane displaying similar tolerability profiles, which furthermore paves the way for extension of endocrine therapy with AIs beyond the time frame of 5 years, although the ideal duration has not yet been established. Side effects of AIs are commonly mild, similar to health conditions related to ageing, and rarely life-threatening. One issue challenging our understanding is that it has been shown that up to 50% of patients report marked alleviation of side effects after they were switched just to another AI, which is not well understood but points to the fact that many of these symptoms have a significant background presence in an age-matched population, and psychological factors also play a role.

The typical adverse events like decrease in BMD and consecutive osteoporosis with a risk elevation of bone fractures are troublesome for patients but preventable and treatable. Long-term medication calls for regular examinations and control of BMD, as well as a good clinical management as soon as problems and danger arise. The addition of bisphosphonates usually is a safe method to prevent bone loss under AI therapy, especially with regard to the fact that the negative effect on bones disappears after completion of therapy. Zoledronic acid not only significantly increased BMD in premenopausal women with HR+ breast cancer but also improved DFS [40].

In contrast to AIs, tamoxifen can be associated with much more profound adverse events which are difficult to prevent and treat, and naturally may have life-threatening consequences. Although endometrial cancer is a rare event, any vaginal bleeding or discharge is an alarming symptom, resulting in costly and unpleasant examinations and avoidable gynecological interventions. Rare and serious adverse events are seen alongside the relatively great number of troublesome but medically harmless side effects, such as hot flashes, hair loss, vaginal dryness, insomnia, and myalgia, which can be satisfactorily managed to a great extent. ABCSG is currently contributing to a questionnaire-based survey (CARIATIDE) to evaluate the influence of supporting educational material

on compliance and retention time under AI therapy in HR+ breast cancer patients. The study will try to explore which patients – and for what reason – fail to be compliant, and how long it takes until they quit AI therapy. CARIATIDE is an international, randomized, multicentre observational study that will include approximately 2,600 patients from more than 200 centers in 18 countries and hopefully will help to identify patients susceptible to compliance failure, to understand the personal reasons of compliance or non-adherence, and to find possibilities to improve communication and the design of information material.

It is of special importance to any clinician to take care of the patient's view, especially concerning the so-called harmless side effects. In a questionnaire-based survey conducted by Garreau et al. [6] on 452 women receiving either tamoxifen or AIs, significant side effects were reported for both tamoxifen and AIs (17.6% used letrozole, 78.6% anastrozole, and 3.8% exemestane). Some side effects were reported to affect up to 84% of patients (muscle aches), but fortunately, the cost of therapy and symptom control was not a barrier to care [6]. Since effectiveness of endocrine therapy is only guaranteed if taken long-term and regularly, education about the accompanying side effects and about the importance of excellent compliance are crucial for any patient's motivation to pursue a successful therapy. Any clinician should emphasize the dialogue with the patient in order to communicate the importance of therapy adherence. In many cases, the question if endocrine therapy is 'pleasant' cannot really be answered in the affirmative. But in order to put the issue into perspective – endocrine therapy has saved the lives of thousands of breast cancer patients so far, and also spared many of them the side effects of chemotherapy. The side effect profile is and should be acceptable for most, especially with regard to a mandatory and effective side effect management and proactive communication by knowledgeable physicians.

Conflict of Interest

None of the authors has any financial interest in or a finacial conflict with the subject matter or materials discussed in this manuscript.

References

1 Fisher B, Dignam J, Bryant J, Wolmark N: Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. J Natl Cancer Inst 2001;93:684–690.

2 Swain SM: Tamoxifen: the long and short of it. J Natl Cancer Inst 1996;88:1510–1512.

3 Hadji P: Menopausal symptoms and adjuvant therapy-associated adverse events. Endocr Relat Cancer 2008;15:73–90.

4 Buzdar A, Howell A, Cuzick J, Wale C, Distler W, Hoctin-Boes G, Houghton J, Locker GY, Nabholtz JM: Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. Lancet Oncol 2006;7:633–643.

5 Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, Bevers TB, Kavanah MT, Atkins JN, Margolese RG, Runowicz CD, James JM, Ford LG, Wolmark N: Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97:1652–1662.

6 Garreau JR, Delamelena T, Walts D, Karamlou K, Johnson N: Side effects of aromatase inhibitors versus tamoxifen: the patients' perspective. Am J Surg 2006;192:496–498.

7 Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, Hoctin-Boes G, Houghton J, Locker GY, Tobias JS: Results of the ATAC (arimidex, tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60–62.

8 Coates AS, Keshaviah A, Thurlimann B, Mouridsen H, Mauriac L, Forbes JF, Paridaens R, Castiglione-Gertsch M, Gelber RD, Colleoni M, Lang I, Del Mastro L, Smith I, Chirgwin J, Nogaret JM, Pienkowski T, Wardley A, Jakobsen EH, Price KN, Goldhirsch A: Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol 2007;25:486–492.

9 Coombes RC, Kilburn LS, Snowdon CF, Paridaens R, Coleman RE, Jones SE, Jassem J, Van de Velde CJ, Delozier T, Alvarez I, Del Mastro L, Ortmann O, Diedrich K, Coates AS, Bajetta E, Holmberg SB, Dodwell D, Mickiewicz E, Andersen J, Lonning PE, Cocconi G, Forbes J, Castiglione M, Stuart N, Stewart A, Fallowfield LJ, Bertelli G, Hall E, Bogle RG, Carpentieri M, Colajori E, Subar M, Ireland E, Bliss JM: Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (intergroup exemestane study): a randomised controlled trial. Lancet 2007;369:559–570.

10 Braithwaite RS, Chlebowski RT, Lau J, George S, Hess R, Col NF: Meta-analysis of vascular and neoplastic events associated with tamoxifen. J Gen Intern Med 2003;18:937–947.

11 Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, Hilfrich J, Kwasny W, Menzel C, Samonigg H, Seifert M, Gademann G, Kaufmann M, Wolfgang J: Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 2005;366:455–462.

12 Chen Z, Maricic M, Pettinger M, Ritenbaugh C, Lopez AM, Barad DH, Gass M, Leboff MS, Bassford TL: Osteoporosis and rate of bone loss among postmenopausal survivors of breast cancer. Cancer 2005;104:1520–1530.

13 Aapro MS: Long-term implications of bone loss in breast cancer. Breast 2004;13(suppl 1):S29–37.

14 Zidan J, Keidar Z, Basher W, Israel O: Effects of tamoxifen on bone mineral density and metabolism in postmenopausal women with early-stage breast cancer. Med Oncol 2004;21:117–121.

15 Kristensen B, Ejlertsen B, Dalgaard P, Larsen L, Holmegaard SN, Transbol I, Mouridsen HT: Tamoxifen and bone metabolism in postmenopausal low-risk breast cancer patients: a randomized study. J Clin Oncol 1994;12:992–997.

16 Cooke AL, Metge C, Lix L, Prior HJ, Leslie WD: Tamoxifen use and osteoporotic fracture risk: a population-based analysis. J Clin Oncol 2008;26:5227–5232.

17 Meunier PJ, Vignot E, Garnero P, Confavreux E, Paris E, Liu-Leage S, Sarkar S, Liu T, Wong M, Draper MW: Treatment of postmenopausal women with osteoporosis or low bone density with raloxifene. Raloxifene study group. Osteoporos Int 1999;10:330–336.

18 Cauley JA, Norton L, Lippman ME, Eckert S, Krueger KA, Purdie DW, Farrerons J, Karasik A, Mellstrom D, Ng KW, Stepan JJ, Powles TJ, Morrow M, Costa A, Silfen SL, Walls EL, Schmitt H, Muchmore DB, Jordan VC, Ste-Marie LG: Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. Breast Cancer Res Treat 2001;65:125–134.

19 Martino S, Cauley JA, Barrett-Connor E, Powles TJ, Mershon J, Disch D, Secrest RJ, Cummings SR: Continuing outcomes relevant to EVISTA: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst 2004;96:1751–1761.

20 Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, McNabb MA, Wenger NK: Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006;355:125–137.

21 Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, Bevers TB, Fehrenbacher L, Pajon ER Jr, Wade JL 3rd, Robidoux A, Margolese RG, James J, Lippman SM, Runowicz CD, Ganz PA, Reis SE, McCaskill-Stevens W, Ford LG, Jordan VC, Wolmark N: Effects of tamoxifen vs. raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA 2006;295:2727–2741.

22 McCloskey EV, Hannon RA, Lakner G, Fraser WD, Clack G, Miyamoto A, Finkelman RD, Eastell R: Effects of third generation aromatase inhibitors on bone health and other safety parameters: results of an open, randomised, multi-centre study of letrozole, exemestane and anastrozole in healthy postmenopausal women. Eur J Cancer 2007;43:2523–2531.

23 Goss PE, Hadji P, Subar M, Abreu P, Thomsen T, Banke-Bochita J: Effects of steroidal and nonsteroidal aromatase inhibitors on markers of bone turnover in healthy postmenopausal women. Breast Cancer Res 2007;9:R52.
24 Mincey BA, Duh MS, Thomas SK, Moyneur E, Marynchencko M, Boyce SP, Mallett D, Perez EA: Risk of cancer treatment-associated bone loss and fractures among women with breast cancer receiving aromatase inhibitors. Clin Breast Cancer 2006;7: 127–132.
25 Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M: Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 2008;9:45–53.
26 Tan AL, Emery P: Role of oestrogen in the development of joint symptoms? Lancet Oncol 2008;9:817–818.
27 Sestak I, Cuzick J, Sapunar F, Eastell R, Forbes JF, Bianco AR, Buzdar AU: Risk factors for joint symptoms in patients enrolled in the ATAC trial: a retrospective, exploratory analysis. Lancet Oncol 2008;9:866–872.
28 Grundy SM: Hypertriglyceridemia, atherogenic dyslipidemia, and the metabolic syndrome. Am J Cardiol 1998;81:18B–25B.
29 Hall G, Collins A, Csemiczky G, Landgren BM: Lipoproteins and BMI: a comparison between women during transition to menopause and regularly menstruating healthy women. Maturitas 2002;41:177–185.
30 Anderson KM, Castelli WP, Levy D: Cholesterol and mortality. 30 years of follow-up from the Framingham study. JAMA 1987;257:2176–2180.
31 Bertelli G, Pronzato P, Amoroso D, Cusimano MP, Conte PF, Montagna G, Bertolini S, Rosso R: Adjuvant tamoxifen in primary breast cancer: influence on plasma lipids and antithrombin III levels. Breast Cancer Res Treat 1988;12:307–310.
32 Liu CL, Yang TL: Sequential changes in serum triglyceride levels during adjuvant tamoxifen therapy in breast cancer patients and the effect of dose reduction. Breast Cancer Res Treat 2003;79:11–16.
33 Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, Boyle P: Overview of the main outcomes in breast-cancer prevention trials. Lancet 2003;361: 296–300.
34 Goss PE: Letrozole in the extended adjuvant setting: MA.17. Breast Cancer Res Treat 2007;105(suppl 1):45–53.
35 Jakesz R, Greil R, Gnant M, Schmid M, Kwasny W, Kubista E, Mlineritsch B, Tausch C, Stierer M, Hofbauer F, Renner K, Dadak C, Rucklinger E, Samonigg H: Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. J Natl Cancer Inst 2007;99:1845–1853.
36 Mamounas EP, Jeong JH, Wickerham DL, Smith RE, Ganz PA, Land SR, Eisen A, Fehrenbacher L, Farrar WB, Atkins JN, Pajon ER, Vogel VG, Kroener JF, Hutchins LF, Robidoux A, Hoehn JL, Ingle JN, Geyer CE Jr, Costantino JP, Wolmark N: Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast and Bowel Project B-33 trial. J Clin Oncol 2008;26:1965–1971.
37 Lin NU, Winer EP: Advances in adjuvant endocrine therapy for postmenopausal women. J Clin Oncol 2008;26:798–805.
38 Partridge AH, LaFountain A, Mayer E, Taylor BS, Winer E, Asnis-Alibozek A: Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. J Clin Oncol 2008;26:556–562.
39 Partridge AH, Wang PS, Winer EP, Avorn J: Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol 2003;21:602–606.
40 Gnant M, Mlineritsch B, Schippinger W, Luschin-Ebengreuth G, Postlberger S, Menzel C, Jakesz R, Seifert M, Hubalek M, Bjelic-Radisic V, Samonigg H, Tausch C, Eidtmann H, Steger G, Kwasny W, Dubsky P, Fridrik M, Fitzal F, Stierer M, Rucklinger E, Greil R, Marth C: Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009;360:679–691.
41 Monnier A: Clinical management of adverse events in adjuvant therapy for hormone-responsive early breast cancer. Ann Oncol 2007;18 (S8):36–44.
42 Sourander L, Rajala T, Räihä I, Mäkinen J, Erkkola R, Helenius H: Cardiovascular and cancer morbidity and mortality and sudden cardiac death in postmenopausal women on oestrogen replacement therapy (ERT).Lancet 1998;352:1965–1969. Erratum in: Lancet 1999;353:330.