Long-term side effects of adjuvant breast cancer treatment

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Chapter 6

The influence of endocrine treatments for breast cancer on health related quality of life: a review

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ABSTRACT

There are several types of endocrine treatments available such as selective estrogen receptor modulators (SERMs), non-steroidal and steroidal aromatase inhibitors, pure ER-antagonists, progestins and luteinising hormone-releasing hormone (LHRH) agonists, which play an important role in breast cancer treatment. The long-term impact of endocrine therapies is increasingly relevant, as patients are treated for years, the number of breast cancer survivors is increasing and more young women are treated with this modality. Health-Related Quality of Life (HRQoL) data can assist in recommendations for future treatment. This review provides a literature-based overview of side effects of hormonal treatment in pre- and postmenopausal breast cancer patients both in the adjuvant and palliative setting and the influence on the HRQoL and sexuality. Relevant clinical studies were identified by using the Medline database, limited to literature in English from between 1977-2006. Side effect profiles of tamoxifen and aromatase inhibitors vary but no significant difference in overall HRQoL was observed. Looking at the balance between efficacy and side effects, the aromatase inhibitors seem to outperform tamoxifen. Tamoxifen increases the incidence of endometrial cancer. Fewer thromboembolic events occur during aromatase inhibitors than with tamoxifen. The incidence of muscle pain and stiffness, joint disorders, and bone fractures was highest during aromatase inhibitors. Although patients may experience a wide range of symptoms, there are only minor differences in HRQoL ratings and they are generally rated as "good". Further research should allow healthcare professionals to tailor their care even more specifically to patients' individual circumstances, providing better disease control while maintaining HRQoL.

INTRODUCTION

Breast cancer is the leading cause of death from cancer in women, but due to earlier diagnosis and improvements in treatment, mortality rates have declined. Steroid hormones, estrogen and progesterone, play a major role in the etiology of breast cancer.[1] The growth of many breast tumors is estrogen-dependent and approximately 70-80% of all breast cancers are hormone-sensitive. Tumors that express estrogen and/or progesterone receptors (ER and/or PgR) are likely to respond to endocrine treatment, which is mostly based on eliminating estrogen production or blocking the estrogen receptor.[2] In premenopausal women the ovary is the major site of estrogen production. In postmenopausal women estrogens are still produced although less, by aromatase-mediated conversion of adrenal androstenedione and testosterone to oestrone and estradiol in extra gonadal tissues, such as subcutaneous fat and muscle tissue. Endocrine therapy plays an important role in breast cancer treatment in pre- as well as in postmenopausal women. It is given as (neo)adjuvant therapy, for metastatic disease and for the prevention of breast cancer. Currently there are many types of endocrine treatment available: selective ER modulators (SERMs), non-steroidal and steroidal aromatase inhibitors, pure ER-antagonists such as fulvestrant, progestins such as megestrol acetate and luteinising hormone-releasing hormone (LHRH) agonists.

Women can experience acute and chronic side effects from endocrine treatment which can affect the Health-Related Quality of Life (HRQoL).[3,4] During adjuvant treatment the long-term impact of endocrine therapies is increasingly relevant, as patients are treated for many years, the number of breast cancer survivors is increasing and an increasing number of younger women are treated by this modality. HRQoL data can assist in recommendations for future treatment.

HRQoL is a broad concept, which takes many factors into account including physical, emotional, sexual, social, and cognitive functions, and symptoms of disease and treatment. All functions and symptoms are assessed by and from the perspective of the patient.[5] Initially trials comparing endocrine treatments paid especially attention to tumor response rates and survival. However, thus non-life threatening side-effects which can be long lasting can be overlooked or underestimated.[6] Therefore it is of interest that many data on side effects and HRQoL have become available over the last years. This information is useful to physicians and patients when making decisions about treatment.[7]

The purpose of this review is to provide a literature-based overview of the side effects of endocrine treatment in pre- and postmenopausal breast cancer

patients both in the adjuvant as in the palliative setting and the influence on the HRQoL, especially sexual functioning.

METHODS

Relevant clinical studies were identified by using the Medline database, limited to literature in English from the period 1977-2006. The following search terms were used: breast cancer, hormonal treatment, endocrine therapy, quality of life, health related quality of life, side effects, adverse events, sexual functioning, sexual dysfunction, psychosexual function, ovarian ablation, ovariectomy, oophorectomy, LHRH analogues, tamoxifen, progestagen, anastrozole, letrozole, exemestane. These search terms were used in varying combinations to identify the most suitable literature. Also, reference lists of selected papers were used to find articles that did not appear in the primary search. Studies were selected only if they were original papers or reviews.

RESULTS

Tamoxifen

Tamoxifen was the firstly used in postmenopausal breast cancer patients in 1963. Tamoxifen is a non-steroidal anti-estrogen, which is used in the adjuvant setting and in metastatic disease for women with hormone receptor positive breast cancer. Its antitumor effect is based on competition with estrogen in binding to its receptor. Tamoxifen can exert an anti-estrogenic as well as an estrogenic effect, depending on the ambient serum estrogen levels (i.e. the menopausal status) and the tissue type.[8] In glandular breast tissue tamoxifen acts as an estrogen antagonist. Tamoxifen is still the agent of choice in the first-line adjuvant and metastatic treatment of premenopausal patients. For postmenopausal women with hormone-receptor positive localized breast cancer, aromatase inhibitors have obtained since recently a role as first line treatment.[9]

Tamoxifen is usually relatively well tolerated. The most frequent side effects are hot flashes, fatigue and nausea. Less frequently observed side effects include uterine bleeding, vaginal dryness, dyspareunia, impaired sexual desire and optical (cataract) problems. Rare are deep venous thrombosis, venous thromboembolism, pulmonary embolism, cardiovascular and ischemic cerebrovascular events. There is an 2-3 fold increased risk of endometrial cancer.[10] Because of the extensive experience with tamoxifen its side effects are

well characterized, especially in postmenopausal women. Several studies have assessed the impact of tamoxifen on HRQoL both in the adjuvant and preventive setting.[11-14]

Tamoxifen versus placebo

Two randomized placebo controlled trials have evaluated toxicity and HRQoL of tamoxifen. In the Wisconsin Tamoxifen Trial, 140 postmenopausal patients were randomly assigned to receive adjuvant treatment with tamoxifen or placebo. More hot flashes and vaginal symptoms were reported by the patients receiving tamoxifen during the 24 months follow-up period. There was no difference between the two groups in incidence of nausea, fatigue, bone pain, joint pain, racing heart, vomiting, depression, sweaty hands, irritability, difficulty sleeping, or gastrointestinal distress. No adverse effects on HRQoL as measured by questionnaires were found.[15]

Results from the HRQoL component of National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP-P1) showed that there was no difference between tamoxifen and placebo in 11,064 healthy women with an increased risk of developing breast cancer, with regard to depression, overall physical or mental quality of life and weight gain after 36 months of treatment. More women on tamoxifen suffered from vasomotor (hot flashes) and gynaecological symptoms (vaginal discharge) compared with the placebo group.[16] There was no evidence that the number of sexually active individuals in the tamoxifen group was reduced since treatment.[16] In a cross-sectional study in 57 breast cancer patients, the sexual functioning after 2 to 24 months of tamoxifen was comparable to baseline data from the NSABP-P1 study.[14] Forty-one (72%) were sexually active. Using a sexual history form and the Breast Cancer Prevention Trial symptom checklist 54% of the participants complained of painful intercourse and nearly a third experienced vaginal tightness. Two other studies found no change in sexual functioning following treatment with tamoxifen in breast cancer patients.[11,13]

All these studies found no differences in HRQoL between placebo and tamoxifen, despite significant increases in vasomotor and vaginal symptoms during tamoxifen.

Tamoxifen versus raloxifene

Raloxifen is a selective ER modulator that is approved by the US Food and Drug Administration for prevention of osteoporosis. The Study of Tamoxifen and Raloxifene, (STAR), is a double blind randomized prevention trial designed to see how raloxifene compares with tamoxifen in reducing the breast cancer incidence in postmenopausal women who are at increased risk of the disease.

Symptoms were collected from a 36-item symptom checklist. HRQoL was measured with the Medical Outcomes Study Short-Form Health Survey (SF-36), the Centre for Epidemiologic Studies-Depression (CES-D) and the Medical Outcomes Study Sexual Activity Questionnaires in a substudy of 1,983 patients. Questionnaires were collected before treatment, every 6 months for 60 months and at 72 months.
No significant differences existed between the tamoxifen (n=973) and raloxifene (n=1,010) groups in patient-reported outcomes for physical health, mental health and depression. The tamoxifen group reported better sexual functioning.
Patients on tamoxifen (n=9,743) reported more gynaecological problems, vasomotor symptoms, leg cramps and bladder control problems, whereas women on raloxifene (n=9,769) reported more musculoskeletal problems, dyspareunia, and weight gain over 60 months of assessments.[17]

Tamoxifen for adjuvant versus advanced breast cancer
Between 1996 and 1998, all patients on endocrine therapy for adjuvant or advanced breast cancer, attending the Edinburgh Breast Unit, were invited to complete a checklist for this specific group.[18] Anastrozole (n=103), megestrol acetate (n=35) and tamoxifen (n=482) were the three most common endocrine therapies. Patients received tamoxifen in the adjuvant (n=429) and advanced setting (n=53). In the adjuvant setting nausea and low energy were reported less frequently, however, increased vaginal discharge and vaginal dryness were experienced more frequently. Data were also analyzed by age group (<49 and >50 years of age) chosen as a proxy measurement of menopausal status. Younger women experienced strikingly more flashes and sweats (74% pre-menopausal versus 53% postmenopausal) and weight gain (61% vs. 39%). The negative effect on libido was also greater in younger women with 40% reporting decreased sexual interest compared with 16% in those over 50 years of age.[18]

Fulvestrant
Fulvestrant is a pure ER antagonist that competitively binds to the ER with a much higher affinity than tamoxifen and without agonistic effects. The down regulation of ER protein results in complete abrogation of estrogen-activated gene transcription.[19] Fulvestrant is used for the treatment of hormone receptor-positive, metastatic breast cancer in postmenopausal women with disease progression following anti estrogen therapy. It is given as a once-monthly intramuscular injection. Fulvestrant is well tolerated: the most common side effects are gastro-intestinal disturbance (40-53%) and hot flashes (19-24%). Less common adverse effects include weight gain, headache, joint pain, sore throat, thromboembolism, and urinary tract infections.[20] No evidence of agonist

activity on the endometrium was observed using ultrasonography of the endometrium. Therefore it is unlikely that fulvestrant is associated with an increased risk of endometrial cancer.[21]

Fulvestrant versus tamoxifen

In a comparative, double blind, randomized trial in postmenopausal women with metastatic breast cancer fulvestrant (n=313) and tamoxifen (n=274) were both well tolerated. The most frequent side effects in both groups were nausea (20.3% fulvestrant versus 22.5% tamoxifen), asthenia (19.4% versus 20.3%), pain (13.9% versus 19.2%) and bone pain (13.9% versus 17%). There was a trend for less gastrointestinal disturbance (nausea, vomiting, diarrhea and constipation) with fulvestrant (37.1% versus 43.2%; $P = .16$) The incidence of hot flashes was slightly lower in the fulvestrant group than in the tamoxifen group (18% versus 25%; $P = .05$).[22]

HRQoL was assessed on day 1, monthly for the first 3 months of treatment, and then every third month up to 12 months using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire. The mean Trial Outcome Index (TOI) scores for each treatment group remained fairly constant during the first year and revealed no difference between fulvestrant versus tamoxifen over time.[22]

Fulvestrant versus anastrozole

In two randomized trials (n=451 and n=400) fulvestrant was compared with the aromatase inhibitor anastrozole in postmenopausal metastatic breast cancer patients whose disease had progressed after prior endocrine therapy.[23,24] Both treatment arms showed equal antitumor activity. A wide range of adverse events was reported by both groups, mostly of mild to moderate intensity. A similar percentage, namely 46% in the fulvestrant versus 40% in the anastrozole group experienced adverse events and about 1% of the patients withdrew from the trials because of adverse events. The most common side effects in these trials were nausea (26% versus 25.3%), asthenia (22.7% versus 27%), pain (18.9% versus 20.3%), vasodilatation (17.7% versus 17.3%) and headache (15.4% versus 16.8%) in the fulvestrant and anastrozole groups, respectively.[25] About 20% of the patients in both groups experienced hot flashes. The incidence of joint disorders, including arthritis, arthrosis and arthralgia was lower in the fulvestrant-treated group than in the anastrozole-treated group (5.4% versus 10.6%) ($P = .0036$).[25] In 4.6% and 1.1% the fulvestrant administration in each trial resulted in mild, transients local reactions.[23,24]

Analysis of QoL data, using the FACT- breast questionnaire, demonstrated that up to disease progression QOL was maintained and there was no difference between the drugs.[23,24]

The higher incidence of joint disorders with the aromatase inhibitor compared with fulvestrant illustrates the value of fulvestrant in a patient population which may be predisposed to musculoskeletal conditions.[26] Fulvestrant is associated with a lower incidence of hot flashes compared with tamoxifen. The tolerability profile and route of administration of fulvestrant may lead to improved compliance and thus better patient outcomes.[26] As for all new agents its overall safety profile will become increasingly clear with ongoing use.[26]

The results of clinical studies comparing fulvestrant with either letrozole or exemestane are not yet available. A clinical trial including fulvestrant in the adjuvant setting is ongoing.

Aromatase inhibitors

Aromatase is a cytochrome-P450 enzyme-complex responsible for the conversion of androgen into estrogen, the final step in the estrogen biosynthesis pathway. Aromatase inhibitors inhibit the conversion of adrenal androgens into estrogens in peripheral adipose tissue and (to a lesser extent) in muscles, which is the main source of estrogens in postmenopausal women. These drugs have, unlike tamoxifen, no partial agonist activity. They are now used in the adjuvant setting and as first line treatment in the metastatic disease. They are under evaluation in combination with LHRH analogue in premenopausal women.[10] In general, aromatase inhibitors are well tolerated. Their most common short-term adverse effects include fatigue, back pain, dyspnoea, headache, and hot flashes. All aromatase inhibitors are associated with an increased risk of osteopenia, osteoporosis, and /or bone fracture. Studies evaluating the efficiency of bisphosphonates to ameliorate this effect are ongoing. Evaluation of potential long-term effects of estrogen deprivation, including cognitive, vascular, skin, and urogenital tract changes, will require longer follow-up.[27] Currently the long-term effects of the aromatase inhibitors are still largely unknown.

Aromatase inhibitor anastrozole versus tamoxifen

The large ATAC trial in 9,366 early breast cancer patients compared the aromatase inhibitor anastrozole alone, or in combination with tamoxifen versus tamoxifen alone in the adjuvant setting for 5 years in postmenopausal women in terms of efficacy and side effects. Disease-free survival after 4 years was superior with anastrozole than with tamoxifen or the combination of these drugs. The combination arm was stopped prematurely because results were equivalent to tamoxifen alone and worse than anastrozole alone.

Compared with tamoxifen, anastrozole was associated with less hot flashes (39.7% tamoxifen versus 34.3% anastrozole), vaginal discharge (11.4% versus 2.8%), vaginal bleeding (8.2% versus 4.5%), ischemic cerebrovascular events (2.1% versus 1.0%), venous thromboembolic events (including deep-vein thrombosis) (1.7% versus 1.0%), and endometrial cancer (0.5% versus 0.1%). However, musculoskeletal complaints (27.8% anastrozole versus 21.3 % tamoxifen) and fractures (5.9% versus 3.7 %) were more common with anastrozole. This increase in fractures seemed to be greatest in the spine, while no increase in hip fractures was seen. The average weight gain, 1.65 kg or 2.5 % over 2 years was similar in all groups. In the anastrozole group (5.1%) less patients withdrew from treatment related adverse events than in the tamoxifen group (7.2%)($P < .0002$).[28] There was no difference between anastrozole and tamoxifen in the incidence of cataracts, ischemic cardiovascular events, fatigue or asthenia, mood disturbance and nausea or vomiting.

A total of 1,021 women were included into the HRQoL subprotocol of this trial. Patients completed the FACT-B plus the Endocrine Subscale (ES) at baseline and 3, 6, 12, 18 and 24 months, or until disease recurrence. No differences between anastrozole, tamoxifen or the combination were found in overall HRQoL during the first 2 years. All three treatment groups showed an HRQoL improvement from baseline over the 2 years assessment period. Between baseline and 3 months of endocrine treatment, mean total ES scores worsened and recovered partially during the 2 years in all groups.[29] Compared with tamoxifen alone, anastrozole results in fewer patients reporting cold sweats, vaginal discharge, irritation, and bleeding, and more patients reporting vaginal dryness, pain or discomfort during intercourse and loss of sexual interest.

Aromatase inhibitors anastrozole for 3 years after 2 years tamoxifen versus 5 years tamoxifen

Data from two prospective, randomized adjuvant trials comparing 3 years of anastrozole after 2 years tamoxifen (n=1,618) versus 5 years of tamoxifen (n=1,606) in postmenopausal women with hormone-sensitive early breast cancer were combined for analysis.[30] Switching to anastrozole after 2 years tamoxifen resulted in less disease recurrences, particularly with respect to distant metastases. There were more fractures ($P = .015$) and fewer thromboses ($P = .034$) in patients treated with anastrozole than in those on tamoxifen for 5 years. More patients experienced nausea ($P = .0162$) and there was a trend towards more reports of bone pain ($P = .0546$) in the anastrozole than in the tamoxifen group.[30]

Aromatase inhibitors letrozole versus placebo

A double blind, placebo controlled trial (MA-17 trial) tested the effectiveness of 5 years of letrozole (aromatase inhibitor) versus placebo in postmenopausal women with breast cancer, who had completed 5 years of adjuvant tamoxifen therapy (n=5,187). Hot flashes (47.2% versus 40.5%), arthritis (5.6% versus 3.5%), arthralgia (21.3% versus 16.6%), and muscle pain (11.8% versus 9.5%) were more frequent in the patients receiving letrozole compared with the placebo group while vaginal bleeding (4.3% versus 6.0%) was less frequent in the placebo group. Fatigue, sweating, constipation, headache, and dizziness were equally distributed between the two groups. The percentage of patients with osteoporosis was similar with 5.8% in the letrozole group and 4.5% in the placebo group *(P* = .07); also the number of fractures was similar.[31] Few women discontinued treatment because of these side effects. Although the patients using letrozole reported more complaints, it is remarkable that even in the placebo group the percentage of patients with complaints is high.

In this study a non significant difference in the rate of cardiovascular events between the letrozole group (4.1%) and the placebo group (3.6%) was found, but a longer follow-up is necessary to rule out the possibility that letrozole has adverse cardiovascular effects in the long-run.[31] Studies on the effects of letrozole on plasma lipids gave conflicting results.[32] In a small study (n=20) a unfavorable effect on the serum lipid profile was found after 8-16 weeks of letrozole therapy.[33] Two studies showed letrozole to have no significant effect on serum lipids after 3 and 6 months.[34,35] The results of a substudy of the MA-17, the MA-17L (n=347) suggest that letrozole does not significantly alter serum cholesterol. HDL cholesterol, LDL cholesterol, triglycerides of Lp(a) in non-hyperlipidemic postmenopausal woman until 3 years.[36] But all the patients in this study were withdrawn from 5 years on adjuvant tamoxifen just prior to entry on this study. Further studies are needed to assess the long-term effects of letrozole on serum lipids in patients without previous tamoxifen therapy.

Of the 5,187 patients randomly assigned in the MA-17 trial, 3,612 participated in the HRQoL substudy: 1,799 were allocated to placebo and 1,813 to letrozole. HRQoL was assessed with the Medical Outcomes Study 36-item Short Form Healthy Survey (SF-36), a multipurpose instrument with 36 items which can be divided over 8 subscales and summarized into two global scores: (the physical and mental component summary) and the MENQOL which assesses the level of discomfort associated with menopausal symptoms. The questionnaires were assessed at baseline, 6 months and annually. The median follow-up was 30 months. Differences between the placebo and letrozole group were found for hot flashes, 17% in the placebo and 22% in the letrozole group (*P* = .0002), and sweating, which occurred in 14% in the placebo and 18% in the letrozole group

($P = .003$). No differences were seen between the groups in mean change scores from baseline for the SF-36 physical and mental component summary scores until 36 months.[32]

Aromatase inhibitor exemestane versus tamoxifen

In the Intergroup Exemestane Study (IES) a double-blind randomized trial, 4,742 postmenopausal women with primary, ER-positive breast cancer were randomized to receive either 5 years tamoxifen or 2-3 years of tamoxifen followed by exemestane, a steroidal aromatase inhibitor.[37] The median follow-up was 30.6 months. Side effects were recorded at 3-months interval during the first year, every 6 months during the second and third year, and annually thereafter. Exemestane was associated with a higher incidence of arthralgia (5.4% versus 3.6%) and diarrhea (4.3% versus 2.3%) than tamoxifen, but gynaecologic symptoms (5.8% versus 9.0%), vaginal bleeding (4.0% versus 5.5%) and muscle cramps (2.8% versus 4.4%) were more common with tamoxifen. The percentage of hot flashes with 42.0% in the exemestane group and 39.6% in the tamoxifen group did not differ. Thromboembolic events occurred more frequently in the tamoxifen group (1.9%) than in the exemestane group (1%). There was also a suggestion of an increased incidence of osteoporosis and visual disturbances associated with exemestane. Fractures were reported somewhat more frequently in the exemestane than in the tamoxifen group (72 patients versus 53 patients, $P = .08$). Other short-term side effects such as nausea and vomiting, fatigue, mood disturbance, headaches and dizziness were noted with equal frequency in both arms.[37]

In a HRQoL subprotocol of the IES, in which 582 patients participated, HRQoL was assessed with the FACT-B questionnaire and an endocrine subscale at 3, 6, 12, 18 and 24 months. Prevalence of severe endocrine symptoms at trial entry was high for vasomotor complaints and sexual problems, which persisted in both groups during the study. No significant differences between groups were seen for any endocrine symptoms apart from vaginal discharge, which was more pronounced during tamoxifen ($P < .001$). The switch from tamoxifen to exemestane neither increased nor decreased endocrine symptoms present after 2 to 3 years of tamoxifen; the switch did also not initiate new symptoms. HRQoL was generally good and stable over 2 years, with no clinically meaningful differences between the groups.

Results indicate that the clinical benefits of exemestane over tamoxifen are achieved without significant detrimental effect on HRQoL.[38]

Table 1. Side-effects in three randomized studies comparing aromatase-inhibitors with tamoxifen or placebo

	ATAC (Baum) [28]		IES (Coombes) [31]		MA-17 (Goss) [37]	
	tamoxifen	**anastrozole**	**tamoxifen**	**exemestane**	**letrozole**	**placebo**
Hot flashes	**39***	**34**	40	42	**47***	**40**
Sweating	–	–	18	19	22	21
Nausea and vomiting	10	10	11	11	–	–
Fatigue	15	16	23	24	30	28
Arthritis	–	–	–	–	**6***	**3**
Arthralgia and musculo-skeletal symptoms	**21***	**28**	**4***	**5**	**21***	**17**
Myalgia	–	–	–	–	**12***	**9**
Bone fractures	**4***	**6**	--		4	3
Osteoporosis	–	–	**6***	**7**	6	4
Vaginal bleeding	8	4	**5***	**4**	**4***	**6**
Vaginal discharge	11	3	–	–	–	–
Endometrial cancer	1	0	–	–	–	–
Gynaecologic symptoms	–	–	**9***	**6**	–	–
Ischemic cardiovascular disease	2	2	–	–	4	4
Ischemic cerebrovascular event	**2***	**1**	–	–	–	–
Venous Thromboembolic disease	**3***	**1**	2*	1	–	–
Cataracts or visual disturbances	4	3	**6***	**7**	–	–
Edema	–	–	–	–	17	16
Constipation	–	–	–	–	10	10
Hypercholesterolemia	–	–	–	–	12	11
Dizziness	–	–	12	12	12	11
Headache	–	–	16	19	18	19
Cramps	–	–	**3***	**4**	–	–
Diarrhea	–	–	**2***	**4**	–	–
Constipation	–	–	–	–	10	10

Aromatase inhibitor anastrozole versus tamoxifen after 2-3 years of tamoxifen

In the prospective randomized Italian Tamoxifen Anastrozole trial (ITA), the efficacy was assessed of switching postmenopausal patients from tamoxifen to anastrozole. After 2 to 3 years of tamoxifen, patients were randomly assigned to receive either anastrozole (n=223) or to continue tamoxifen (n=225), for a total of 5 years. Switching to anastrozole improved disease free and local recurrence-free survival. Patients on anastrozole, experienced more than one adverse event (47 versus 32 patients, $P = .06$) and overall, more events than in the tamoxifen group (203 versus 150 events, $P = .04$). Compared with patients who continued on tamoxifen more patients in the anastrozole group experienced gastrointestinal symptoms (2.7% versus 7.9%, $P = .03$) and lipid metabolism disorders (4.0% versus 9.3%, $P = .04$). Tamoxifen treatment resulted in reduced plasma cholesterol levels and anastrozole showed to be lipid neutral. Therefore it is likely that the changes in serum lipids in the anastrozole group are a result

of the effects of tamoxifen withdrawal. Switching to anastrozole resulted in a reduction of gynaecologic side effects, including endometrial carcinoma (11.3% versus 1.0%, *P* = .0002). There were no differences in the incidence of musculoskeletal disorders or bone fractures; however these results are preliminary, based on a small number of events after 3 years of tamoxifen treatment, so differences might arise after longer follow-up. In approximately 40% of the patients switching from tamoxifen to anastrozole was associated with some new side effects.[39]

Table 2. HRQoL and differences in side-effects in three randomized studies comparing aromatase-inhibitors with tamoxifen or placebo as adjuvant treatment for breast cancer.

study	tool	N	treatment	duration	HRQoL	side effects	
ATAC.[29]	FACT-B plus Endocrine Subscale (ES)	1021	anastrozole, tamoxifen,or combination for 5 years	2 years	no difference	***Tamoxifen*** hot flashes ischemic CVE any venous TD deep-venous TD	***Anastrozole*** musculoskeletal disorders bone fracture
MA-17[32]	Medical Outcomes Study (SF-36) MENQOL	3612	5 years of letrozole versus placebo after completion of 5 years tamoxifen	2 years	no difference	***Placebo*** vaginal bleeding	***Letrozole*** hot flashes arthritis arthralgia myalgia
IES.[38]	FACT-B questionnaire plus endocrine subscale	582	5 years tamoxifen or 2-3 years of tamoxifen followed by exemestane	2 years	no difference	***Tamoxifen*** vaginal bleeding gynaecologic symptoms TD	***Exemestane*** arthralgia osteoporosis visual disturbances cramps diarrhea

CVE = cerebrovascular event; TD = thromboembolic disease

Aromatase inhibitor letrozole versus tamoxifen

The randomized, double blind Breast International Group (BIG 1-98) study compared two adjuvant endocrine therapy regimens in postmenopausal women with hormone-receptor-positive breast cancer. This analysis compared letrozole (n = 4,003) to tamoxifen (n = 4,007) after a median follow-up of 25.8 months.[40] This study found a significant reduction in the risk of distant recurrences with letrozole, as compared with tamoxifen.

More bone fractures occurred during letrozole compared with tamoxifen (5.7% versus 4.0%, $P < .0001$). Also arthralgia was more frequent in the letrozole than in the tamoxifen group (20.3% versus 12.3%, $P < .001$). As compared with tamoxifen, letrozole was associated with fewer thromboembolic events (1.5% versus 3.5%, $P < .001$). Hot flashes and night sweats were experienced more frequently during tamoxifen than letrozole (33.5% versus 38.0%, $P < .001$ and 13.9% versus 16.2%, $P = .004$). In the letrozole group less vaginal bleeding (3.3% versus 6.6%, $P < .001$) and fewer invasive endometrial cancers (0.1% versus 0.3%, $P < .18$) were found.

In the tamoxifen group the mean cholesterol values decreased more than in the letrozole group. A total of 43.6% patients on letrozole and 19.2% patients on tamoxifen had hypercholesterolemia reported at least once during treatment. The overall incidence of adverse cardiovascular events of grade 3-4 was similar in both groups but more women on letrozole experienced grade 3-4 cardiac events (2.1% versus 1.1%, $P < .001$).

Aromatase inhibitors are becoming increasingly important in the management of early breast cancer. Several studies have compared aromatase inhibitors to tamoxifen in the adjuvant setting. Differences in trial design, type of aromatase inhibitors, patient selection (previous adjuvant chemotherapy, positive axillary nodes) and follow-up duration make HRQoL comparison of the trials complicated. In general aromatase inhibitors are well tolerated. Switching to an aromatase inhibitor after tamoxifen offers the opportunity to continue adjuvant therapy for longer than 5 years, while problems of tolerability that may arise from the partial agonist effects of tamoxifen are circumvented.[30] Third generation aromatase inhibitors seem to have specific effects on vasomotor and gynaecologic symptoms and sexual functioning, but no major adverse effects on overall HRQoL.[7] The long-term side effects of the aromatase inhibitors are not known, and it is possible that the toxicity profile will change with the accumulation of additional data.[41] The possible influence of these long-term side effects on HRQoL is also unknown.

Advanced breast cancer

Aromatase inhibitor anastrozole versus tamoxifen

Anastrozole (n=511) and tamoxifen (n=506) were compared as first line therapy for advanced breast cancer in a randomized double blind study in postmenopausal women. Both drugs were well tolerated by most patients. Fewer thromboembolic events (5.3% versus 9.0%) and vaginal bleeding (1.0% versus 2.5%) were observed during anastrozole. Hot flashes were reported by 27.5% of the patients on anastrozole versus 24.1% on tamoxifen.[42]

Tamoxifen versus aromatase inhibitors

In a prospective study menopausal symptoms were analyzed 1 and 3 months after the start of first-line tamoxifen (n=83) or aromatase inhibitors (letrozole n=61, anastrozole n=10, exemestame n=10) in postmenopausal breast cancer patients (postmenopausal status was defined as cessation of menses for more than 1 year). A total of 80% received adjuvant hormonal treatment and 20% were treated for advanced disease. Both treatment regimens increased the occurrence ($P < .0001$) and severity ($P = .014$) of hot flashes. Musculoskeletal pain ($P = .0039$) and dyspareunia ($P = .001$) occurred more frequently during aromatase inhibitors, while patients on tamoxifen experienced a decrease in sexual interest ($P = .0001$).[6]

Comparing aromatase inhibitors: letrozole versus anastrozole

In a small multicentre, randomized, investigator-blinded, cross-over study, anastrozole and letrozole were evaluated for HRQoL, toxicity and patient's preference. Seventy-two postmenopausal women, who had previously received tamoxifen, were randomized to either anastrozole or letrozole for 4 weeks followed by 1-week washout, and then crossed over to the alternative treatment for 4 weeks. HRQoL was measured with the FACT-general scale together with the breast cancer (FACT-B) and endocrine (FACT-ES) subscales. HRQoL mean total scores were better during letrozole compared with anastrozole. Overall, fewer patients on letrozole experienced adverse effects than on anastrozole. Letrozole induced less lethargy (8% versus 19%), nausea (10% versus 22%), joint pain (3% versus 11%), abdominal discomfort (3% versus 11%), appetite (2% versus 14%) and headache (5% versus 14%). Anastrozole was not superior for any of the adverse effects. Patient's preference was in favor of letrozole (68% versus 32%) due to better overall HRQoL, less nausea, fewer hot flashes and less abdominal discomfort. A strong correlation between patients' preference and HRQoL on each drug was found.[43]

Progestins

Synthetic progestins such as megestrol acetate and medroxyprogesterone act similarly as the natural hormone progesterone. The mechanism of action in breast cancer has not been fully elucidated. The most common side effects of progestins included increased appetite and weight gain, fluid retention and edema, hypertension, tremor, menorrhagia and thromboembolic episodes. Less frequently reported are muscle cramps, sweating, nausea with or without vomiting, and hypercalcemia.[44] Response rates to progestins can be increased with dose escalation, but the side effects are also dose dependent.[44,45] Megestrol acetate is the most frequently prescribed progestin. Several studies

have evaluated HRQoL during megestrol acetate versus the newer aromatase inhibitors in advanced breast cancer.

Megestrol acetate versus formestane

Megestrol acetate was compared to the aromatase inhibitor formestane as second line treatment in postmenopausal patients with advanced breast cancer (n=177) after disease progression on tamoxifen. HRQoL was compared to both arms using the linear self-assessment scales (LASA) for 6 times during the first year of treatment. HRQoL did not differ between the two groups.[46]

Megestrol acetate versus anastrozole

Two phase III trials compared the tolerability and clinical efficacy of two doses of anastrozole (1 mg and 10 mg/day) to megestrol acetate (40 mg orally four times daily). Buzdar and co-workers recruited 386 and Jonat et al 378 postmenopausal women with advanced breast cancer who progressed after tamoxifen treatment. In both studies HRQoL was assessed by the Rotterdam Symptom Checklist. With the exception of weight gain and edema in the megestrol acetate group compared with anastrozole 1 mg, there were no differences between these groups in side-effects.[47] In the study of Buzdar et al individuals in the anastrozole group had better HRQoL scores. Patients in the 1 mg group had superior physical scores compared with the megestrol group and those in the 10 mg group had better psychological scores than patients treated with megestrol acetate ($P < .025$).[48]

Megestrol acetate versus letrozole

Megestrol acetate (40 mg/day) and two letrozole doses (0.5 mg/day and 2.5 mg/day) in postmenopausal breast cancer patients were compared in a double-blind, randomized trial in 602 patients.[49]

More patients on megestrol acetate experienced weight increase (13.4% versus 3.0% and 3.5%), increased appetite (11.4% versus 2% and 1%), dyspnoea (37.8% versus 23.8% and 23.1%), and vaginal bleeding (8% versus 3% and 0.5%) than patients treated with either dose of letrozole. More patients on 2.5 mg letrozole experienced headache (10.6%) than patients on megestrol acetate (4.5%) or letrozole 0.5 mg (2.5%). The Karnofsky performance status and HRQoL (using the questionnaire EORTC QOL-C3 version 2.0) were obtained each month for the first 6 months and at 9 and 12 months. Treatment groups were similar for the Karnofsky performance status and global HRQoL scale based on an exploratory longitudinal analysis. In general, the decreases from baseline in performance status were less in those on letrozole, while HRQoL scores were comparable, with roughly half of the scales favoring letrozole treatment and half favoring megestrol acetate treatment.[49]

In each of these comparative studies with megestrol acetate, the aromatase inhibitors appear to cause fewer side effects, while weight gain on megestrol acetate is the only side effect consistently reported in all these studies. The difference in HRQoL reported between megestrol acetate and the aromatase inhibitors are small but mostly in favor of the aromatase inhibitors.

Ovariectomy

Surgical ovariectomy in premenopausal women, currently performed by laparoscopy, is a relatively straightforward endocrine therapy with little peri-operative morbidity, but it is invasive and irreversible. Ovarian ablation has long been established as an effective therapy for premenopausal women with metastatic breast cancer. In women below 50 years of age with early breast cancer, ablation of functioning ovaries improves long-term survival, at least in the absence of chemotherapy.[50] Further evidence obtained in randomized studies is needed concerning the effects of ovarian ablation in the presence of other adjuvant treatments. Early ovariectomy has many well-documented side-effects related to the premature menopause, such as hot flashes, sexual dysfunction, urogenital atrophy, bone demineralization, and possibly, cardiovascular problems. Apart from reducing estrogen production, ovarian ablation (combined with salpingo-oophorectomy) also reduces the risk of developing ovarian or tubal cancer. Younger women with breast cancer might belong to a breast-ovarian cancer family either with or without a *BRCA1/2* mutation and hence have an increased risk of ovarian cancer. Although surgical ovarian ablation is the oldest endocrine treatment for breast cancer no HRQoL studies have been performed comparing this modality with other endocrine treatment. One study compared HRQoL impact of chemotherapy and oophorectomy mostly performed by radiation (98%). This study showed that the influence of ovarian ablation and chemotherapy on HRQoL were clearly different; overall the ovarian ablation was much milder except for hot flashes and sweats.[51]

LHRH-analogue

LHRH agonists downregulate the LHRH production by the hypothalamus effectively and produce a "medical ablation" of ovarian function which is reversible on discontinuation of therapy.[52] In premenopausal women the combined use of LHRH and tamoxifen is a therapeutic option. The rationale for this combination is that having effectively rendered the patients postmenopausal with LHRH, the effect of peripheral estradiol can be inhibited by tamoxifen.[53] Besides, tamoxifen treatment in premenopausal women may induce

hyperstimulation of the ovaries with supra-physiological levels of estradiol, which can be prevented by simultaneous down regulation of the ovaries with LHRH agonists. Goserelin is the most extensively investigated compound.[52] Treatment with LHRH agonists is associated with menopausal side effects such as hot flashes, mood changes and sexual problems.

LHRH-analogue versus tamoxifen versus LHRH-analogue combined with tamoxifen

From 1990 to 1996, a prospective, multicentre, randomized adjuvant study in premenopausal women (n=2,710) with invasive breast cancer was conducted with goserelin (ZIPP-trial). After primary surgery, with or without adjuvant chemotherapy (cyclophosphamide, methrotrexate, fluorouracil), patients were randomized to four groups receiving the LHRH analogue goserelin, tamoxifen, goserelin plus tamoxifen or no systemic therapy (control group) for 2 years.[54]
In 293 patients who participated in this study the effect of endocrine therapies on physical and psychological symptoms were studied. Patients at seven assessment points completed a questionnaire consisting of the Hospital Anxiety and Depression Scale and a symptom checklist, over 3 years after randomization. The main result was that endocrine therapy had differential effects only in patients who had not received CMF. Goserelin was associated with the highest level of menopausal symptoms. The patients who received tamoxifen alone reported more hot flashes than the control group. Patients in the goserelin and in the combination group (goserelin plus tamoxifen), however, reported the highest levels of vasomotor symptoms, probably due to the abrupt menopause caused by the LHRH analogue.[55] A side study examined several aspects of sexuality through The Relationship and Sexuality Scale, a 19-item questionnaire. This non-validated questionnaire was completed at the same time points as the other questionnaires. Patients treated with chemotherapy had a higher level of sexual dysfunction even at 3 years since randomization, than patients who received no chemotherapy, independent of endocrine treatment. It is well known that chemotherapy induces a postmenopausal status due to ovarian ablation, which can be reversible in younger women. Goserelin alone or in combination with tamoxifen also had a negative effect on most parameters of sexuality among patients not receiving chemotherapy from 1 to 2 years after inclusion, as compared with those who received no endocrine treatment. Tamoxifen alone did not increase the level of sexual dysfunction.[11]
In an earlier study in 318 pre- and perimenopausal advanced breast cancer patients in which goserelin with or without tamoxifen was investigated for objective tumor response, time to progression and overall survival, patients reported no increased complaints by the addition of tamoxifen to goserelin. In

the goserelin alone group, slightly more patients (33%) had received adjuvant chemotherapy compared with the combination group (25%). Hot flashes (74% versus 72%), vaginal discharge (13% versus 18%), vaginal pain (both 18%), and adverse effect on sexual activity (15% versus 10%), were similar in both groups.[56]

DISCUSSION

Over the last years in addition to analyses of antitumor effects more attention has been paid to the impact of endocrine therapy on patients' HRQoL.[57] Knowledge of the impact of endocrine therapies on the HRQoL in cancer patients will enable clinicians to provide better information to their patients when treatment decisions must be made. It will also help to evaluate the cost/benefit ratio of therapeutic interventions.[4] All currently available endocrine therapies have side-effect profiles, which can affect patient-rated HRQoL outcomes. Although the side effects of the various endocrine treatments differ and patients may experience a wide range of symptoms, there are only minor differences in HRQoL ratings as measured by questionnaires and the HRQoL is generally rated as "good".

Although the side effect profiles of tamoxifen and aromatase inhibitors vary, no significant difference in overall HRQoL was observed in two large adjuvant studies comparing aromatase inhibitors, and tamoxifen.[29,38] Even an aromatase inhibitor versus placebo did not show a difference in overall HRQoL.[31] The minimal changes in HRQoL as reported suggest that many symptoms experienced by women who participated in these studies are age- and menopause related and not dependent on any endocrine medication. In addition, many studies included patients that had received prior chemotherapy therefore side-effects in this setting cannot be attributed to endocrine therapy alone.[57] Patients also may have adapted so well to their new situation that they accept the changes that have occurred as the price that has to be paid for their present health (response shift). In the past, a range of different instruments have been used to assess side effects of endocrine therapy and its influence on HRQoL and sexuality and this makes direct comparison between studies difficult. In some studies non-validated questionnaires have been used or validated questionnaires that have not been validated for breast cancer patients. An advantage of the latter is, however, that they allow direct comparisons with a healthy population. Obtaining adequate baseline data that can be longitudinally compared to treatment data may ensure an accurate estimation of the extent of changes and to conclude if they are due to the treatments given.

Looking at the balance between efficacy and side effects, the aromatase inhibitors seem to outperform tamoxifen. Tamoxifen is known to increase the incidence of endometrial cancer and fewer thromboembolic events occur in patients treated with aromatase inhibitors than in those who received tamoxifen.[30] However, the incidence of muscle pain and stiffness, joint disorders and arthralgia was highest in the aromatase inhibitor groups [25,37] Aromatase inhibitors also cause an increased incidence of bone fractures compared with tamoxifen.[30] The effectiveness of adding bisphosphonates to prevent osteopenia and osteoporosis to aromastase inhibitors is still under evaluation. Data on the long-term impact of hormonal therapies on bone demineralization and cardiovascular risk in younger patients is still limited for the newer agents. More efforts should be made to generate sufficient data on the extent and reversibility of changes in bone and lipid metabolism, and finding ways to prevent or repair these unwanted side effects. In patients at low risk for breast cancer recurrence and therefore a small chance of benefiting from these adjuvant treatments, the incidence, severity, duration and reversibility of side effects are even more relevant in selecting the optimal treatment.[58,59] Five years of adjuvant endocrine therapy is now standard, and 10-15 years treatment is currently being investigated. Further research in this setting should allow healthcare professionals to tailor their care even more specifically to patients' individual circumstances, providing better disease control while importantly maintaining HRQoL.[60]

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