Effects of estrogen deprivation due to breast cancer treatment

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Abstract

Breast cancer is one of the main life-threatening diseases that a woman may have to face during her lifetime. The increasing incidence of breast neoplasia reported over the last few decades has led to widespread screening of women resulting in early diagnosis. One common but challenging question for most doctors, after the surgical excision of the lesion, is determination of the ideal adjuvant therapy for their patients for the achievement of maximum life expectancy with the best quality of life.

Since the beginning of the last century, the knowledge that breast cancer arises from hormone-responsive tissues has long made use of hormone-blocking agents in the beneficial treatment of breast neoplasia. The discovery of new molecules with endocrine actions has rendered the use of adjuvant therapy in a tailor-made pattern too complicated, as these agents have a different mode of action, different adverse effects and probably different indications.

The aim of the present review is to clarify these issues, analyzing the mechanism of action of available drugs and their actions on specific areas of uncertainty: cognitive function, cardiovascular system, urogenital tract, bone metabolism, weight gain, hot flushes and premature menopause. Regarding the efficacy of adjuvant therapy, there has been particular focus on the multiple hormonal-induced consequences of each regimen in order to provide the clinician with the available data for choosing the ideal therapy for the patient.

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Introduction

Adjuvant therapy in breast cancer consists of hormonal therapy with or without chemotherapy given after surgical excision of the tumor. The goal of hormonal adjuvant treatment in early breast cancer is the inhibition of estrogen trophic function in malignant cells (Doisneau-Sixou *et al.* 2003). Initially, hormonal therapy was based on surgical ablation (ovariectomy, adrenalectomy, hypophysectomy) and the use of androgens, progestagens or combined estrogen–progestagens limited to postmenopausal women (Paterson & Russel 1959). High-dose estrogen was generally considered the endocrine therapy of choice for postmenopausal women with breast cancer, and diethylstilbestrol (DES), the first orally active artificial estrogen, was commonly administered for the therapy of advanced breast cancer before

the introduction of contemporary endocrine therapy. A major advance was made with the introduction of tamoxifen (a selective estrogen receptor modulator (SERM) which was the first commercially available anti-estrogen agent), considered as the standard treatment for patients with breast cancer positive in estrogen receptors (ERs), because it causes fewer side-effects than DES (Smith & Good 2003). Megestrol acetate, in North America, and aminoglutethimide, in Europe, had previously been the traditional second-line therapies after tamoxifen in advanced breast cancer. Other hormonal approaches, such as the use of aromatase inhibitors, fulvestrant (a selective downregulator of ERs), gonadotropin-releasing hormone (GnRH) analogues, raloxifene (SERM), oophorectomy, and chemical and radiological ovarian ablation, have been applied as alternative methods in ER-positive patients.

Background

Efficacy of adjuvant hormonal treatment

Adjuvant endocrine therapy is recommended for nearly all women with a breast tumor that expresses ERs or progesterone receptors. The first critical overview of data unequivocally demonstrated that tamoxifen was associated with a highly significant improvement in relapse-free and overall survival (Early Breast Cancer Trialists' Collaborative Group 1990). Its efficacy in the treatment and prevention of ER-positive breast cancer was indisputably established 8 years later (Early Breast Cancer Trialists' Collaborative Group 1998a) in all age groups that were studied (47% reduction in recurrence after 5 years and 26% reduction in mortality after 10 years). Accordingly, 5 years of tamoxifen is the standard adjuvant treatment for patients with hormone receptor-positive early breast cancer irrespective of age, menopausal status or tumor stage (Early Breast Cancer Trialists' Collaborative Group 1998a).

To date, results in the adjuvant setting, regarding aromatase inhibitors, are available only for anastrozole, which was tested in the world's largest individual cancer trial: the Anastrozole, Tamoxifen Alone or in Combination (ATAC) trial. Anastrozole achieved significantly longer disease-free survival than tamoxifen as a first-line adjuvant therapy at a median follow-up of 33 months (Baum *et al.* 2002). The efficacy re-analysis at a median follow-up of 47 months (Buzdar *et al.* 2003) confirmed the continued disease-free survival benefit in the anastrozole-treated group.

Letrozole is being investigated in several large adjuvant trials: the North-American Intergroup Trial and the Breast Cancer International Group trial (comparing tamoxifen for 2 years followed by letrozole for 3 years, versus letrozole for 2 years followed by tamoxifen for 3 years) (Goss 2001). No results have yet been presented from these two studies. The first results from an exemestane adjuvant trial reported that, after 2 to 3 years of tamoxifen therapy, switching to exemestane was more effective than continuing tamoxifen therapy for the remainder of the 5 years of treatment (Coombes *et al.* 2004). Significantly, an important recent study, designed to investigate the potential effects of continuing estrogen deprivation with letrozole after 5 years of tamoxifen treatment, indicated that the rate of disease-free survival was significantly higher in the letrozole-treated group than in the placebo-treated group (Goss *et al.* 2003). The above unexpected outcomes led to the early termination of the study after a median duration of follow-up of 2.4 years. However, in this limited period, no significant difference in overall survival was demonstrated. There is only fractional documentation on the effects of aromatase

inhibitors in premenopausal patients; thus, such therapy is currently restricted to postmenopausal women.

The Early Breast Cancer Trialists' Collaborative Group (1996) has confirmed that in women (50 years of age), overall survival and recurrence-free survival significantly improved after ovarian ablation. Combination chemotherapy has also been found to substantially improve the long-term relapse-free and overall survival of both premenopausal and postmenopausal women up to the age of 70 years (Early Breast Cancer Trialists' Collaborative Group 1998b).

The availability of a treatment producing a reversible castration acceptable to many patients in the adjuvant setting and the evidence supporting an endocrine mechanism of cytotoxic chemotherapy in premenopausal patients led to the hypothesis that GnRH analogues could be of benefit in the treatment of hormonal-sensitive breast cancer. It has been indicated that a reversible castration over 2–3 years with a GnRH analogue is comparable in terms of disease-free and overall survival to treatment with six courses of cyclophosphamide, methotrexate and fluorouracil (CMF) chemotherapy (Boccardo *et al.* 2000, Castiglione-Gertsch *et al.* 2000) among premenopausal patients with hormone receptor-positive disease. Radiotherapy at the ovaries seems to produce a two-third reduction in local recurrence of breast cancer; however, the absolute benefit is diminished because of the disadvantage of permanent amenorrhea (Early Breast Cancer Trialists' Collaborative Group 2002, del Moral *et al.* 2002).

The hypothesis of combined endocrine treatment has been addressed in the ATAC trial. The combination arm with anastrozole plus tamoxifen did not show a better outcome than the tamoxifen-alone arm. In fact, as mentioned, the outcome was inferior to that in the anastrozole-alone arm. Furthermore, according to the findings of the Austrian Breast and Colorectal Cancer Study Group trial, there were no significant differences between the use of tamoxifen-alone versus tamoxifen plus aminoglutethimide for 5 years of treatment in postmenopausal women with early-stage breast cancer in terms of either disease-free or overall survival (Schmid *et al.* 2003).

Efficacy of hormonal treatment in advanced disease

As second-line therapy after tamoxifen for ER-positive metastatic breast cancer, all three aromatase inhibitors have been shown to be superior to progestin therapy because of their better safety profile and favorable impact on survival (Buzdar *et al.* 1998, Dombernowsky *et al.* 1998). In recent years, it has been found that aromatase inhibitors are superior to tamoxifen in the first-line treatment of advanced disease (Bonnetterre *et al.* 2000).

In an overview of trials comparing treatment with a GnRH analogue with or without tamoxifen among premenopausal patients with advanced disease, the patients treated with concurrent tamoxifen showed a significantly higher objective response rate and a longer progression-free and overall survival, compared with those treated with the GnRH analogue alone (Klijn *et al.* 2001). In women with metastatic disease and positive ERs, chemotherapy seems to act more efficaciously against rapidly progressing tumors (Wilcken *et al.* 2003).

Fulvestrant has been approved in the USA for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer following progression on anti-estrogen therapy. Patients with hormone-sensitive breast cancer who have responded to tamoxifen may receive additional benefit from a second endocrine agent (fulvestrant, megestrol acetate, aromatase inhibitors), following progression or relapse after tamoxifen therapy (Morris & Wakeling 2002). Similar response rates and time to progression have been reported (Bross *et al.* 2002) in postmenopausal women with a previous response to endocrine therapy when an aromatase inhibitor or fulvestrant were administered.

Mechanisms of action

Tamoxifen appears to have both agonist and antagonist estrogenic actions in various organs and inhibits the growth of breast tumors by competitively antagonizing estrogen binding to its receptor. Tamoxifen decelerates the proliferation of breast cancer cells by inhibiting their progression from the G1 phase of the cell cycle and induces apoptosis. The cellular effect of the linkage of a SERM with the receptor is a complex procedure and depends on the specific isoform (α or β) of the receptor. Thus, SERMs act as an antagonist when combined with ER- β but can also function as an agonist through ER- α (Hall & McDonnell 1999). Moreover, a number of co-regulator peptides which seem to interfere with the receptor's function, acting as either a positive or a negative regulator, have been discovered. The potential role of these proteins, both co-activators and co-repressors, is still under investigation but they seem to modulate the biological responsiveness of the target cell of a SERM in various ways (Riggs & Hartman 2003).

Among postmenopausal women, the agonistic action of the SERM raloxifene in bone has attracted much interest, especially after the early termination of the Women's Health Initiative (WHI), because of the reported elevated risk in breast cancer and the increased occurrence of cardiovascular events with the use of hormone replacement therapy (HRT) (Chlebowski *et al.* 2003, Wassertheil-Smoller *et al.* 2003). Although many

questions posed by the above study remain unanswered, raloxifene appears to be a reasonable alternative in postmenopausal women for the prevention of osteoporosis. Raloxifene, beneficial to HRT because of its tissue selectivity, seems to act as an estrogen antagonist in breast cancer (Cummings *et al.* 1999). Preliminary results of the study of raloxifene and tamoxifen (STAR) trial will add much to our awareness of the potential use of raloxifene in the prevention of breast cancer (Vogel *et al.* 2002). However, to date, raloxifene is approved for postmenopausal osteoporosis in patients without a history of breast cancer, or in breast cancer patients only after their treatment, including adjuvant therapy, has been completed (raloxifene prescribing information (package insert) 1999; Eli Lilly and Co., Indianapolis, IN, USA). Aromatase inhibitors markedly suppress plasma estrogen levels in postmenopausal women by inhibiting or inactivating the enzyme aromatase. This enzyme is responsible for the conversion of androgenic substrates to estrogens (specifically, the synthesis of estrone from the preferred substrate androstendione and estradiol from testosterone) (Smith & Dowsett 2003). The third-generation aromatase inhibitors can be classified with respect to their chemical structure as steroidal or non-steroidal agents. The two main members of non-steroidal aromatase inhibitors are letrozole and anastrozole.

Exemestane is an irreversible, steroidal, specific third-generation aromatase inactivator. Maximal estrogen suppression occurs after the first 2–3 days of therapy and estrogen levels return to baseline in 10–14 days. Highly selective blockade of aromatase does not interfere with the production of other steroids (e.g. adrenal corticosteroids, aldosterone and androgens). Evidence suggests that tumor progression is not due to a loss of estrogen suppression but to newly developed tumor resistance, including acquired hypersensitivity of some tumor cells to estrogens. Differences in the mechanism of action in this class of agents may contribute to the apparent lack of cross-resistance between steroidal (e.g. exemestane) and non-steroidal (e.g. letrozole and anastrozole) aromatase inhibitors (Kvinnslund *et al.* 2000). So far, exemestane has been approved only for the treatment of postmenopausal women with recurrent breast cancer in deterioration after tamoxifen (Lonning 2000). Findings from ongoing studies will determine the role of exemestane in early breast cancer and its potential role in breast cancer prevention (Jones & Jones 2000).

Excessive or inappropriate aromatase expression was demonstrated in adipose fibroblasts surrounding breast carcinoma. Intra-tumoral activity of aromatase in the majority of breast tumors is well established and such activity contributes substantially to intra-tumoral estrogen levels. It has been proved that anastrozole, letrozole

and exemestane noticeably inhibit this action (Miller & Dixon 2001). In conclusion, the relative clinical significance of the potential direct role of all the pharmacological agents used for adjuvant therapy in breast cancer on the intra-tumoral hormonal milieu remains unknown.

GnRH analogues suppress secretion of pituitary gonadotropins and this results in the reduction of estrogen production. These molecules bind to specific receptors consisting of seven transmembrane domains on pituitary gonadotropic cells, stimulating a rapid Ca^{2+} mobilization from internal stores. GnRH analogues differ from native GnRH in their 100- to 200-fold higher binding affinity to the receptors and in their pharmacokinetic parameters. GnRH agonists lead to an intense release of stored luteinizing hormone and follicle-stimulating hormone (the 'flare-up effect'), which results in a temporary increase of ovarian-produced estradiol, followed by a more prolonged decrease of pituitary hormone secretion (desensitization). On the other hand, recently introduced GnRH antagonists induce immediate reduction of gonadotropin levels, presenting a promising option in the goal of diminishing circulated estrogen (Kiesel *et al.* 2002). It is of interest that GnRH analogues, in addition to their essential action of suppressing the secretion of pituitary gonadotropins, might play other roles. Expression of GnRH receptors in both healthy (Kottler *et al.* 1997, Grundker *et al.* 2002) and cancer breast cells (Harris *et al.* 1991, Grundker *et al.* 2002) presume a possible autocrine/paracrine mechanism of the action of GnRH analogues in these tissues by modifying cell function(s). Stimulation of these receptors by GnRH analogues leads to activation of various intracellular mechanisms, which are different in normal and cancer cells. However, these potential anti-cancer properties of GnRH analogues are still hypothetical.

The development of fulvestrant as a selective antagonist of estrogen was based on the understanding that tamoxifen-like drugs are not devoid of estrogen-like actions and that their intrinsic partial agonist effects may have undesired consequences in various tissues. In contrast to the partial agonists, studies have demonstrated that multiple changes in ER function after fulvestrant treatment (i.e. impaired dimerization, increased turnover and disrupted nuclear localization) contribute to the blockade of estrogen action (Howell *et al.* 2000). Moreover, it is reported (Pink & Jordan 1996) that fulvestrant markedly reduces cellular levels of ERs in pointed contrast to the stable or increased ER levels associated with tamoxifen.

Finally, alternative therapeutic approaches consist of the supplementary use of various chemotherapeutic regimens and occasionally radiotherapy, which act directly on ovaries, suppressing the production of

estrogens. Combination of the above strategies tends to be the current state of the art in the issue of treating patients with ER-positive cancers even at early stages of the disease (Table 1).

Skeletal effects

Two isoforms of estrogenic receptors have been identified in bones: α -receptors (ER- α), which are expressed mostly in the developing cortical bone, and β -receptors (ER- β) which are expressed in the developing cancellous bone (Bord *et al.* 2001). Tamoxifen reduces bone demineralization due to its confirmed agonist estrogenic action (Love *et al.* 1994, Powles *et al.* 1996) and this is a disadvantage in premenopausal patients. Bone density was slightly improved in postmenopausal women who received tamoxifen for 2 years; however, almost half of this benefit was lost after 5 years of continuous administration, which is the usual duration of tamoxifen therapy. Regarding the fracture risk, the results of the available reports are conflicting (Riggs & Hartman 2003). Anastrozole, by lowering the circulating estrogen levels, appears to be associated with a higher incidence of total and vertebral fractures (5.9% and 0.7% respectively) than tamoxifen (3.7% and 0.3% respectively) according to the results derived from the ATAC trial (Baum *et al.* 2002). It is of great interest that in the same study the reported risk for hip fractures was 0.4%, irrespective of the agent administered. This could possibly be explained by the different concentrations of ERs in the various types of bones, which result in a different total effect of each regimen in vertebral bones and a similar effect in the hip region. In addition, aromatase inhibitors have been considered responsible for the clinical syndrome of polyarthralgia, which appears to be unrelated to increased bone resorption (ATAC trial). Arthralgia with similar features has been mentioned in cases of women during the postpartum period and in early menopause, when circulating estrogens are rapidly decreased. Based on this observation, it has been suggested that estrogen has a possible suppressive role in the progression of rheumatoid diseases (Wluka *et al.* 2000, Baum *et al.* 2002). In a short-term 3-month postmenopausal human volunteer experiment, exemestane or letrozole was administered daily at the usual anticancer doses of 25 and 2.5 mg respectively to each of 20 women, and a placebo was given to 20 women representing a control group (Goss *et al.* 2002). Over this short time-period, bone biomarkers of formation and resorption were similar in the women given exemestane or placebo (Goss *et al.* 2002). In contrast, there was a sharp increase in bone turnover in those given letrozole over the same time-period. It has been assumed from studies in ovariectomized rats that bone metabolism is protected by the androgenicity of

Table 1 Common hormonal treatment in ER-positive breast cancer

Substance	Action	Dose	Current indication	Promising but preliminary results	Future directions
Tamoxifen	Antagonizing estrogen binding to its receptor	20 mg/day p.o.	All stages of breast cancer alone or in combination with other agents		
Megestrol acetate	Anti-estrogenic action	160 mg/day p.o.	Second-line therapy in postmenopausal patients with advanced breast cancer previously treated with tamoxifen	Third-line therapy after failure of aminoglutethimide	
Raloxifene	Antagonizing estrogen binding to its receptor	60 mg/day p.o.	Postmenopausal osteoporosis	Chemoprevention	
Anastrozole	Non-steroidal third-generation aromatase inhibitor	1 mg/day p.o.	Postmenopausal women with advanced disease or in adjuvant therapy (particularly if tamoxifen is contraindicated)	Neoadjuvant therapy and chemoprevention	Use in combination with chemotherapy
Letrozole	Non-steroidal third-generation aromatase inhibitor	2.5 mg/day p.o.	Postmenopausal women with advanced disease	Continuing hormonal therapy after 5 years of tamoxifen Neoadjuvant therapy Chemoprevention Preoperative therapy	Use in combination with chemotherapy
Exemestane	Steroidal-type aromatase inhibitor	25 mg/day p.o.	Second-line agent in metastatic disease	First-line therapy	Combination with cytostatic agents Neoadjuvant therapy
Fulvestrant	'Pure' anti-estrogen	250 mg/month i.m.	Second- or third-line agent in postmenopausal women with disease progression following anti-estrogen therapy	Preoperative therapy to downstage primary breast cancer	Replacement of tamoxifen

exemestane and its metabolite 17-hydroexemestane (Goss *et al.* 2004).

It is possible that early-stage breast cancer patients could benefit from bisphosphonates by ameliorating the cancer treatment-related bone loss. Even more importantly, most women with newly diagnosed breast cancer are at risk of osteoporosis because of their age, and trends in adjuvant hormonal therapy indicate that osteoporosis will become a greater clinical problem in the future. Although raloxifene is approved for osteoporosis prevention and therapy, its use following 5 years of tamoxifen adjuvant therapy is not recommended. This is based on the fact that raloxifene and tamoxifen are similar agents and 10 years of tamoxifen use has been associated with more recurrences and deaths than 5 years of tamoxifen (Fisher *et al.* 2001).

Adequate information is currently available about the skeletal consequences of adjuvant chemotherapy. Chemotherapy-treated women who maintained ovarian

function had normal bone mineral density (Headley *et al.* 1998), whilst a decrease in bone density was, as expected, reported in women with functional suppression of the ovaries (Shapiro *et al.* 2001). These women could be at risk for early development of osteoporosis and the use of bisphosphonates may be beneficial (Saarto *et al.* 1997, Partridge *et al.* 2001, Shapiro & Recht 2001). However, the maintenance of bone density depends only in part on estrogen. The implementation of exercise and a multifaceted protocol of drug therapy for bone remodeling immediately following chemotherapy-induced treatment (bisphosphonates, calcium and vitamin D supplementation) are producing encouraging results (Twiss *et al.* 2001). The need for early bone mineral density assessments and close monitoring has therefore been suggested in this high-risk population of women. The American Society of Clinical Oncology (ASCO) guidelines published in November 2003 outline the appropriate measures for each risk-group category (Hilner *et al.* 2003).

Because bisphosphonates have effectively reduced the development and progression of bone metastases in advanced breast cancer (Kanis *et al.* 1996, Theriault *et al.* 1999) current research has focused on bisphosphonates as an adjuvant therapy (Diel *et al.* 1998, Saarto *et al.* 2001, Powles *et al.* 2002). The trials conducted provide conflicting data on this potential role of bisphosphonates among patients with no evidence of distant metastases after definitive local surgery. Thus, starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction is not recommended and the presence or absence of bone pain should not be a factor in initiating bisphosphonates (ASCO; Hilner *et al.* 2003). Consequently, it remains uncertain as to whether bisphosphonates are beneficial and further investigation is needed to clarify whether bisphosphonates can influence the development of bone metastases and improve survival in early-stage breast cancer.

Primary menopause and HRT in women with breast cancer

Menopausal symptoms are an important source of morbidity in patients with breast cancer. The potential use of HRT in such patients is controversial, although recent reports have failed to confirm any increased risk of recurrence in women using HRT for breast cancer treatment, whereas the benefits in the quality of life reported were significant (Vassilopoulou-Sellin *et al.* 1999, O'Meara *et al.* 2001). However, existing clinical data do not yet suffice to evaluate the efficacy of this strategy (Cobleigh *et al.* 1994, Shapiro & Recht 2001) and further randomized studies are needed to reassess the issue of HRT in women with breast cancer. A systematic review of 11 controlled and uncontrolled trials concluded that HRT has no significant effect on breast cancer recurrence; however, the reported findings were based on observational data subject to a variety of biases (Col *et al.* 2001). Until the WHI study was published, mortality due to breast cancer in HRT users was thought to be the same or even lower than in non-users and this has been attributed to earlier diagnosis and better prognosis. However, WHI reports revealed more advanced disease in HRT users (Chlebowski 2003, Wassertheil 2003), which is in contradiction to most published observational studies (Antoine *et al.* 2004).

Reasonably, HRT could be given in combination with tamoxifen in premenopausal women with increased levels of estrogens in order to eliminate the anti-estrogenic effect of tamoxifen (e.g. hot flashes). In addition, women with primary menopause due to chemotherapy could gain advantages from the supplementation of estrogens. About 5–10% of breast cancers are caused by an inherited

mutation of either the BRCA1 or BRCA2 gene (Loman *et al.* 2001) and the great majority of these patients do not express ERs. Prophylactic mastectomy and oophorectomy are the most effective treatments in carriers of these mutations (Armes *et al.* 1999). This specific group of women could benefit from receiving HRT (Armstrong *et al.* 2004); however, available data are as yet insufficient (Riggs & Hartman 2003).

The older age of patients and the duration of chemotherapy are positively correlated with increased risk of primary menopause. The time-course of menopause varies from 2 to 16 months from the beginning of chemotherapy. Permanent menopause, as a side-effect of CMF, is more frequently reported compared with the combination of cyclophosphamide and doxorubicin. Whether the use of taxanes is associated with such an adverse effect on the patient's ovaries remains uncertain (Partridge *et al.* 2001, Shapiro & Recht 2001). Reduction of libido has been mentioned in women undergoing adjuvant treatment, which seems to be related more often to the use of chemotherapy regimens rather than tamoxifen. Decreased libido in a patient with breast cancer seems to be a complex process which depends on an integration of potential mechanisms including neurotoxicity, estrogen reduction, impaired quality of life and possibly depression. Consequently, it is incorrect to assume that the observation mentioned above is solely an endocrine disorder (Ganz *et al.* 1998, Shapiro & Recht 2001).

The urogenital tract

It is well known that lack of estrogens results in atrophy of the urogenital system and dyspareunia. There is supporting evidence that estrogen replacement therapy in postmenopausal women is associated with increased risks of uterine cancer. Due to its local agonist role, tamoxifen is correlated with an approximately 2- to 2.5-fold rise in the relative risk of endometrium cancer in the first 1 or 2 years of treatment and this risk is approximately quadrupled in trials of 5 years of tamoxifen administration (Early Breast Cancer Trialists' Collaborative Group 1998a, Fisher *et al.* 1998, Bergman *et al.* 2000). However, the agonist effect of tamoxifen in the uterus, with regard to the risk of endometrium cancer, is time, dose and age dependent (Fisher *et al.* 1998, Bergman *et al.* 2000, Baum *et al.* 2002, Chen *et al.* 2003). In this regard, vaginal bleeding, which is commonly observed in these women, requires further investigation (Fisher *et al.* 1998, Riggs & Hartman 2003). In most cases, the detected tumor is not aggressive (i.e. low grade stage 1), and is rarely a sarcoma with a poor prognosis (Bergman *et al.* 2000, Baum *et al.* 2002). It has recently

been suggested that tamoxifen differentially regulates human telomerase reverse transcriptase (hTERT) gene expression in breast and endometrial cancer cells, and this activity has been associated with the presence of an estrogen-sensitive element in the hTERT gene. The hypothesis of direct involvement of tamoxifen in the regulation of cancer cell growth may be associated with its opposite effects in the breast and uterus (Grundker *et al.* 2002). A reasonable approach for these patients is a routine pelvic examination and prompt evaluation of abnormal vaginal bleeding by endometrial biopsy.

Cardiovascular effects

SERMS mimicking estrogen actions reduce the level of low density lipoprotein cholesterol and increase high density lipoprotein levels, without increasing the concentration of triglycerides (Bruning *et al.* 1988, Saarto *et al.* 1996). In contrast, the estrogen-lowering effects of aromatase inhibitors have an adverse effect on blood lipids, according to a small, short-term study (Elisaf *et al.* 2001). The available data are insufficient to evaluate the long-term effects discussed.

The cumulative cardiovascular effect of tamoxifen seems to be related to inflammatory, thrombotic and anti-atherogenic activities. Tamoxifen has been associated with increased relative risk of venous thromboembolism (1.5- to 3-fold rise), but the total risk remains small (Cutuli *et al.* 1995, Meier & Jick 1998, Baum *et al.* 2002). On the other hand, analyses of individual trials have suggested that long-term adjuvant treatment with tamoxifen may result in substantial reduction of cardiac morbidity (Rutqvist & Mattsson 1993).

The concurrent combination of chemotherapy and tamoxifen has been associated with an increased risk of thromboembolism when compared with tamoxifen administration alone (Saphner *et al.* 1991) among postmenopausal patients. Patients receiving anastrozole had a significantly lower incidence of venous thromboembolism compared with the patients receiving tamoxifen (2.1% and 3.5% respectively) (Baum *et al.* 2002).

Cognitive effects

ER- α receptors are mainly located in the hypothalamus, while ER- β receptors are distributed in almost the entire brain (hippocampus–amygdala) and thus are strongly associated with superior cerebral functions and memory. Several potential mechanisms have been proposed including: (a) accumulation of the production and secretion of neurotransmitters; (b) direct action on the nervous cells and stabilization of the structure of cell membrane; (c) prevention of cerebrovascular ischemia; and (d) alteration

of the serum lipoprotein profile. Experimental studies on animals have shown that estrogen promotes both the enlargement and the maturation of the dendritic spines of nervous cells located in the hypothalamus and hippocampus.

Additionally, an increase in the number of synapses has been observed in sections of the brain which are topographically associated with learning. It has been suggested that estrogen affects memory-linked processes in postmenopausal women by altering brain activation patterns in specific brain regions (Shaywitz *et al.* 1999). Another study has indicated that the use of estrogen in postmenopausal women may delay the onset and decrease the risk of Alzheimer's disease (Tang *et al.* 1996). Despite the above findings in postmenopausal women, it remains unknown as to whether the status of diminished estrogen levels after the use of adjuvant treatment translates to clinical impairment.

To date, studies focused on the long-term outcomes of tamoxifen have not furnished sufficient information to enhance our knowledge about its impact in the cognition and behavior of the treated patients (Winer *et al.* 2002). A double-blind randomized trial (Multiple Outcomes of Raloxifene Evaluation (MORE) study), which is currently investigating the multiple outcomes of another SERM, raloxifene, is expected to clarify several issues. Local estrogen biosynthesis modified by aromatase activity in the brain may be important in the regulation of various cognitive and hypothalamic functions, but little is known about the clinical expression of this hypothesis. However, improvement in cognitive function (based on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) QLQ-C30 quality-of-life test) of patients treated with retrozole has been reported (Phillips & Bernhard 2003).

Regarding adjuvant chemotherapy, several authors have attempted to estimate its potential side-effects on memory, concentration and attention by using questionnaires and psychological tests (Schagen *et al.* 1999, Partridge *et al.* 2001). However, some of the examined patients were co-treated with tamoxifen, thus making it difficult to reach a conclusion. It is of interest that these studies failed to determine further cognitive impairment in the subgroup of patients who received additional tamoxifen (Schagen *et al.* 1999). Moreover, approximately one-third of the examined women complained of cognitive disorders, a factor which failed to be recorded in the tests performed. Nevertheless, it is clear that the severity of symptoms positively correlates with the use of increased drug doses (van Dam *et al.* 1998, Schagen *et al.* 1999, Partridge *et al.* 2001). The role of taxanes in the neurotoxicity of peripheral nerves has been well established, but their role in the central nervous system has yet

to be investigated (Shapiro & Recht 2001). In conclusion, the observed discrepancy between subjective symptoms and objective findings in several studies may have resulted not only from the insufficient objectiveness of the methods used, but also from individual variations in the way the patients were mentally and psychologically influenced during the painful procedure of chemotherapy (Kattlove & Winn 2003).

Hot flushes

It has been confirmed that the use of tamoxifen increases hot flushes in women with breast cancer (17% vs 7.5% of the placebo-treated group), but this adverse effect seems to be eliminated in the late postmenopausal period (Riggs & Hartman 2003). Initial results of the ATAC trial have shown a comparative risk for the appearance of hot flushes with anastrozole and tamoxifen (34.3% and 39% respectively) (Baum *et al.* 2002). In women unable or unwilling to take hormonal therapies such as in breast cancer (Biglia *et al.* 2003), several non-hormonal alternatives have been proposed, namely clonidine (an α_2 -presynaptic adrenergic agonist), venlafaxine, paroxetine and gabapentin (selective serotonin reuptake inhibitors) (Pandya *et al.* 2000). Many of the women studied were taking concurrent tamoxifen and all of these agents have demonstrated efficacy in reducing hot flushes (Sicat & Brokaw 2004). Tamoxifen is converted to 4-hydroxy-tamoxifen and other active metabolites by cytochrome P450 enzymes and this conversion is reduced by the co-administration of a selective serotonin reuptake inhibitor (Stearns *et al.* 2003). Thus, hot flushes in breast cancer survivors should no longer be considered untreatable as there are pharmacologic treatments available that can help alleviate this problem.

Weight gain

Aromatase expression in adipose tissue primarily accounts for the extraglandular (peripheral) formation of estrogen and increase in body weight in obese postmenopausal women. From this viewpoint, obesity has been associated with an increase in the recurrence of breast cancer, and thus it is considered as a potential risk factor in the progression of the disease (Camoriano *et al.* 1990, Partridge *et al.* 2001, Shapiro & Recht 2001). Premenopausal women undergoing a prolonged therapeutic regime and those receiving prednisone are the most likely to gain weight. Appearance of symptoms of depression and a parallel mild increase in body weight has been associated with tamoxifen, but the reported cases are few. Regarding chemotherapy, the usual weight increase is 2–6 kg and is milder with doxorubicin and

cyclophosphamide use than with CMF treatment. Possible causes are suggested as being the reduction of physical exercise, increased food intake, primary ovarian failure and possible alterations in the basic metabolism (Demark-Wahnefried *et al.* 1993, 1997).

New breast cancer events

Early findings on the use of SERMs (tamoxifen and raloxifene) as a prophylaxis against ER-positive breast cancer have demonstrated hopeful, though preliminary, results (Cuzick *et al.* 2003, Early Breast Cancer Trialists' Collaborative Group 1998a). Evidence based on the National Surgical Adjuvant Breast and Bowel Project (NSABP) has been developed for the use of tamoxifen as a risk-reducing agent in women at high-risk for breast cancer (49% decrease among high-risk women) (Fisher *et al.* 1998). This use of tamoxifen was supported by European tamoxifen trials which, however, included both high- and low-risk women (Cuzick *et al.* 2003). However, it is crucial to identify the subgroup of high-risk healthy women for whom the risk/benefit ratio is sufficiently positive. It is suggested that maximal clinical benefit and minimal side-effects could be derived from the preventive use of tamoxifen in younger premenopausal women, who are less likely to have thromboembolic sequelae and uterine cancer (Chlebowski *et al.* 2002). The MORE trial, which evaluated the use of raloxifene to prevent osteoporosis, found (after 40 months of follow-up) that the risk of invasive breast cancer decreased by 76% (Cummings *et al.* 1999). Among postmenopausal women, some investigators reported that measurements of estradiol level could help to identify women belonging to the potential 'high-risk' group, who may benefit most from the use of raloxifene (Cummings *et al.* 2002). In 1999, the NSABP initiated a second study (which is currently under way), the STAR trial, in order to evaluate the use of raloxifene, by comparison with tamoxifen, as a potential preventive agent in breast cancer. This study was designed to recruit approximately 19 000 women and will investigate the efficacy of both regimens in reducing the incidence of primary breast cancer in high-risk healthy women (Vogel *et al.* 2002).

Another major issue in the topic of ER-positive breast cancer is the optimal management of postmenopausal patients who have completed the classical 5 years of adjuvant tamoxifen therapy. An important recent study, designed to investigate the potential effects of continuing estrogen deprivation with an aromatase inhibitor (letrozole), indicated that the rate of disease-free survival was significantly higher in the letrozole-treated group than in the placebo-treated group (Goss *et al.* 2003). Distant metastasis, ipsilateral recurrences and new contra-lateral

Table 2 Side-effects of available agents in adjuvant therapy of breast cancer

Side-effect	Tamoxifen	Raloxifene	Megestrol acetate	Fulvestrant	Letrozole	Anastrozole	Exemestane	GnRH analogues	Chemotherapy
Hot flushes	++	++	+	+	+	+	N/A	+	+
Uterine discharge	+	↔	+	↔	↔	↔	N/A	–	↔
Endometrial cancer	+	↔	N/A	?	↔	↔	N/A	?	↔
Prevention in new breast cancer events	+	+	N/A	?	+	+	N/A	N/A	?
Thromboembolism	++	↔	+	↔	↔	↔	N/A	↔	+ ²
Arthralgia	↔	↔	N/A	+	++	++	?	↔	↔
Bone density	+	++	N/A	?	–	–	?	–	?
Cognitive function	?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	?
Weight gain	+	?	++	+	↔	↔	N/A	N/A	+
Ovarian suppression	↔	↔	↔	↔	↔	↔	↔	+ ¹	++

+, drug increases this effect; –, drug decreases this effect; ↔, no change; N/A, no data available; ?, conflicting or insufficient data; +¹, preserve ovarian function from chemotherapy-induced infertility; +², attenuated by concurrent treatment with tamoxifen.

breast cancers were implicated as breast cancer events. The above unexpected outcomes led to the early termination of the study after a median duration of follow-up of 2.4 years. However, in this limited period, no significant difference in overall survival was demonstrated (Goss *et al.* 2003).

Conclusions

Side-effects of adjuvant therapy for breast cancer must be taken into account when planning therapy (Table 2), but the clinical experience of many decades has shown that the benefits far outweigh the risks. In conclusion, patients receiving anastrozole have a significantly lower incidence of hot flushes, vaginal bleeding, vaginal discharge and venous thromboembolism, and a significantly higher incidence of musculoskeletal symptoms and fractures than those receiving tamoxifen. However, tamoxifen remains the ‘golden standard’ in adjuvant early ER-positive breast cancer treatment. Preliminary findings from the use of aromatase inhibitors are promising, but longer follow-up investigations are required before a final ‘benefit vs risk’ assessment can be made for this endocrine option. Use of anastrozole has not yet been recommended as a first-line therapy in premenopausal women (American Society of Clinical Oncology Technology Assessment (Winer *et al.* 2002)), but anastrozole treatment is currently a useful alternative, especially in patients who do not tolerate tamoxifen.

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