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Editorial

Endocrine treatment and prevention of breast and gynaecological cancers

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From epidemiological studies, we know that total oestrogen exposure increases a woman's risk for developing breast and endometrial cancer. However, sex steroids do not damage epithelial cell DNA directly, but stimulate or inhibit epithelial cell proliferation resulting in a modulating role on tumour growth, developmental progression, invasion and metastasis. The last three decades have brought a variety of modalities that can intervene between oestrogen—and the oestrogen receptor (ER). In late stage cancer, such agents are able to stop tumoral growth in some oestrogen-sensitive tumours, while in early stage disease, after surgical removal of the tumour, adjuvant endocrine therapy may protect the remaining tissue and distant organs from becoming cancerous. Endocrine agents also have a promising role in the prevention of cancer in healthy 'at-risk' women.

Recent developments in ER research, endocrine prevention and treatment of breast and gynaecological cancers prompted the Flemish Gynaecologic Oncology Group to organise their third international meeting last December in Brussels, Belgium. Their first international meeting in 1997 was on 'tamoxifen and the uterus' [1], the second in 1999 on 'the oestrogen receptor (ER) and Selective Oestrogen Receptor Modulators (SERMs) in breast and gynaecological cancers' [2]. This time, the subject was 'endocrine prevention and treatment of gynaecological and breast cancers'. The organisers invited experts from all over the world to discuss these new developments. The following topics were discussed: An update on ER- research and its modulators, their effect on the uterus and the latest developments on the current role of endocrine prevention and treatment in the adjuvant and metastatic setting of oestrogen-dependent gynaecological and breast cancers.

In this supplement of the *European Journal of Cancer*, each invited presentation is summarised as extended abstracts with relevant references; selected oral presentations are grouped and poster presentations are summarised in abstract form.

1. Oestrogen receptor research

Endogenous sources of postmenopausal oestrogens were discussed [3]. Oestrogens mainly originate from adrenal androgens by extragonadal conversion of androstenedione and testosterone in peripheral tissues through local activity of aromatase, which is body weight and age dependent; postmenopausal oestrogen production by the ovary has recently been challenged [4]. Other peripheral enzymes such as 17 ß-hydroxysteroid dehydrogenase type 1/2 and sulphatase are also important [5], as are binding properties of sex-hormone binding globulin. The genomic sequences and exons required for tissue-specific (placenta versus peripheral fat versus bone versus intra tumoral tissue) aromatase expression have recently been described [6]; more specific aromatase inhibitors may soon be developed to avoid potential side-effects like musculo-skeletal disorders and lipid changes related to a low 'overall' oestrogen environment as seen with the third generation aromatase inhibitors (e.g. anastrozole, exemestane, letrozole). Genes for steroidogenic enzymes show polymorphisms in the general populations and some have linked this to an inter individual cancer risk, but a lot of the evidence remains to be proven; in general, no weak or inconsistent relationships with clinical phenotypes were evident in these observational studies [7]. Evidence was presented that among African women, homozygous

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carriers of the CYP 17 A2 allele expose their endometrium to a stronger oestrogenic stimulation contributing to the pathobiology of uterine leiomyomas [8].

ER function is still poorly understood, but a better understanding may lead to novel strategies and targets for breast cancer prevention and treatment. Breast cancers have been classified based on variations in gene expression patterns derived from cDNA micro-arrays. An ER-positive group could be divided into at least two subgroups, each with a distinctive expression profile with significant differences in clinical outcome. An ER-α with increased sensitivity to oestrogens has been described in benign and (pre)malignant breast tissue leading to a markedly increased proliferation at sub-physiological levels of oestrogen. As there is a growing importance for endocrine therapy in women with hormone-responsive cancers, the correct measurement of steroid hormone receptors remains a cornerstone in the management of breast cancer.

The semi-quantitative immunohistochemical scoring system measures the pres-ence of the steroid receptor as adequately as the now largely abandoned biochemical method. It combines the % of cells with a nuclear staining and the intensity of staining. A zero score for both ER and PR means unresponsiveness and an increasing score reflects a better chance of response to endocrine therapy. One such system uses the H score (0–300); it counts 100 cells in three different high-power fields and each nucleus is given a value between 0 and 3 depending on the intensity of ER expression. Other subjective scoring systems are in use and have been validated. The importance of quality assurance of both interpretation and methodology were stressed [9].

Gustafsson [10] put the latest developments in ER ß research into perspective. The two ER subtypes vary in structure and their encoding genes are on different chromosomes. ER ß plays an essential role in regulating vascular function and blood pressure. In normal breast tissue, ER ß has a physiological role in oestrogen signalling. Breast cancer tissue that is only positive for ER ß shows a higher proliferation rate compared with tissues having a high expression of both ERs. ER ßcx seems to be responsible for a more aggressive behaviour. The presence of this isoform could result in anti-oestrogen resistance in ER-positive breast cancers. Until now, several other variants of ER ß with a different affinity for oestrogen binding have been described. Maybe there is a place for anti-ER ß treatment [10], but not all investigators believe ER ß plays a major regulatory role in cancer.

ER ß expression has also been investigated in tissue from endometrial and ovarian cancers [11]. Compared with levels of ER α, ER ß was significantly lower. There seems to be a stable ratio between both receptors in normal and non-metastatic cancerous tissue. This ratio is significantly different in tissue from a metastatic deposit where ER ß seems to be upregulated. Progesterone receptor (PR) expression has been less well studied. Both PRs, (PRA and PRB) are present in endometrial cancer and decrease with tumour dedifferentiation. Loss of PRA expression precedes loss of E-cadherin during dedifferentiation and leads to a more invasive potential of endometrial cancer both in tissue culture and in tissue from patients with endometrial cancer [12]. Evidence exists that the interleukin-1 (IL-1) system also plays a role in endometrial malignancies with a negative correlation between IL-1 and tumour grading. This negative correlation suggests that the non-physiological expression of IL-1 contributes to the more invasive and malignant behaviour of poorly differentiated endometrial cancers [13].

An update on the mechanisms of action of SERMs was also presented [14]. These agents antagonise oestrogens in some tissues such as the breast and uterus and mimic its action in others such as the bone and liver. The mechanisms for tissue selectivity are complex. Different ligands induce different three-dimensional structures within the ligand-binding domain of the receptor leading to the exposure of different surfaces to the nuclear receptor co-activators or repressors [15]. The balance of co-repressors and co-activators influence the transcriptional activity of the activated ER. After activation, this complex directly binds oestrogen response elements of DNA or numerous other genomic response units adding additional challenges to current efforts to elucidate SERM mechanisms of action. There are now four different categories of SERMs available (most still in trials) and probably more to come. The winning molecule will be the one that has an improved anti-oestrogenic effect on the breast compared with tamoxifen, but does not stimulate the endometrial layer. Most compounds tested so far have been abandoned because of deleterious effects on the endometrium and because they are no better than the generally well-tolerated tamoxifen. The different categories are: the triphenylethylenes, the benzothiophenes, the naphthalenes and other compounds like TSE-424, ERA-923 and EM-800 [34].

There also exists an oestrogen or ligand independent ER activation. Recent developments also show that the ER interacts directly with the growth-factor-signalling pathway at every level of signal transduction resulting in synergism between ER and growth factors. This has been documented both in normal breast development and, importantly, in breast cancer progression and anti-oestrogen resistance. Growth factors are capable of increasing the activity of protein kinases that phosphorylate different sites on the ER, which leads to transcription even in the absence of ER activation. This may explain resistance to SERMs [16] and not to other hormonal treatments that do not have to modulate the ER to be active. Women with an ER-positive breast cancer with amplified c-erB2 are, according to

a small, as yet unconfirmed, study, more resistant to tamoxifen than to letrozole [17]. Probably, time is ready to initiate an adjuvant breast cancer study which finds out whether inhibiting such growth factors might overcome tamoxifen resistance.

2. Endocrine prevention of breast and gynaecological malignancies

Carcinogenesis is a multi-stage process. Tumour initiation starts 20–40 years before the cancer becomes clinically apparent. Results from prevention measures intervening in tumour initiation will take more than a generation to obtain. Tumour promotion takes between 0 and 5 years, but intervening in late stage development will be effective within a couple of years. As such, prevention equals treatment of the undetectable lesion [18]. The science behind endocrine prevention was presented [19,20]. Breast cancer initiates in the undifferentiated lobules type 1 (Lob 1), which are composed of three cell types: highly proliferating cells that are ER-negative, non-proliferating cells that are ER+, and very few (<1%) ER+ cells that proliferate. The differentiation process, from lobular type 1 to type 4 is hormone-dependent and induced by an early full-term pregnancy. It is associated with lower cell proliferation, a lower amount of ER and a more efficient DNA repair capacity making tissues refractory to carcinogenesis. Lob 1 is the less developed and Lob 3 the most differentiated, with the highest number of ductules per lobular unit. Through a paracrine system, ER-positive cells stimulate the ER-negative population after being activated by oestrogens. This dual system disappears with age (and probably due to prolonged low oestrogen exposure) and is characterised by a population of ER-positive cells that do proliferate and as such become a target for carcinogenesis and prevention; breast cancer cells do contain ER-positive cells with a higher proliferation index compared with atypical epithelial hyperplasia and ductal carcinoma *in situ* (DCIS).

The *BRCA* gene plays a role in repairing DNA damage induced by the oestrogen-ER interaction, explaining in part why carriers of the mutated *BRCA* gene have an increased breast cancer risk at an earlier age and why early pregnancy does not protect against the development of breast cancer. In addition, in this population many of the strategies for breast cancer prevention involve oestrogen deprivation. Rebbeck [21] reported on the Prevention and Observation of Surgical End Points (PROSE) study showing how bilateral prophylactic oophorectomy (including the fallopian tubes) will reduce breast cancer in 50–70% and ovarian cancer in over 95% of women with a *BRCA 1/2* mutation. In this population, the risk of breast cancer is increased by early parity and is decreased by breast-feeding and by cigarette smoking. It is important to consider the acute and long-term effects of induced menopause in young women at high risk for breast cancer. So far, there are no convincing data on whether hormonal replacement therapy is hazardous in carriers of *BRCA* mutations with remaining breast tissue. Robson [22] presented data on the potential protective effect of anti-oestrogens such as tamoxifen. Although the number of patients with a genetic risk included remains small, the protective effect may be more pronounced in *BRCA-2* mutation carriers than in *BRCA-1* patients, which may be a reflection of their respective ER state.

Long-term data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 trial comparing tamoxifen with placebo in 13388 women aged 35 years or over at an increased risk of developing breast cancer because of age, family history or other factors were presented [23]. The incidence of both DCIS and invasive cancers was reduced by 50% from 6.8 to 3.4 breast cancers/1000 women years. The greatest benefit was observed in women with lobular carcinoma *in situ* (LCIS) and atypical hyperplasia [24]. He compared his data with the ongoing Italian [25] and Royal Marsden trial [26] that both included fewer patients with, especially for the Italian trial, a lower breast cancer risk. In the extended follow-up data from the Italian trial (81.2 months), breast cancer was diagnosed in 79 women; 45 of 2708 controls and 34 of 2700 on tamoxifen, but the difference was not significant and no patient died of her breast cancer. Those on hormone replacement therapy had a higher breast cancer risk which tamoxifen seems to protect against, but the incidence of breast cancer in each arm was small [25,32]. The ongoing NSABP P2 or STAR trial, a randomised prevention (S)tudy of (T)amoxifen (A)nd (R)aloxifene in 22000 postmenopausal women at increased breast cancer risk, 12000 of whom have already been randomised, was also highlighted as were future studies with goserelin in combination with raloxifene (RAZOR trial), a bisphosphonate (GISS trial) and a tibolone (TIZER) trial in very high risk (those with a *BRCA1* or *BRCA2* mutated genes) premenopausal women.

With tamoxifen, the decreased incidence of invasive and non-invasive breast cancers and osteoporotic fractures need to be balanced against the increased incidence of endometrial cancers, strokes, pulmonary emboli, deep vein thrombosis and eye problems like cataracts. The HOT study will compare 5 years of tamoxifen 5 mg with placebo in hormone replacement therapy users [32]. Preliminary results from International Breast Intervention Study (IBIS)-I trial, testing tamoxifen versus placebo in over 7000 high-risk pre- and postmenopausal women with a median follow-up of over 4 years were recently presented at the EBCC 2002 meeting in Barcelona [30]. Tamoxifen, and this confirms findings from previous studies, showed a significant

protective effect against DCIS, but for invasive disease there only was a trend towards protection against invasive ER-positive breast tumours. The side-effect profile was similar to that in other trials using tamoxifen. The number of thrombo-embolic events in this setting—probably preventable by a temporary drug stop in case of long-term immobilisation—were of particular concern. IBIS-II was also outlined. This prevention study launches in September 2002 and will compare tamoxifen 20 mg daily with anastrozole 1 mg daily in 4000 women with DCIS and anastrozole 1 mg daily versus placebo in 10000 high-risk postmenopausal women.

Other compounds such as isoflavones, tyrosine kinase inhibitors/anti-epidermal growth factor receptor (EGFR) antibodies, cyclo-oxtgenase (COX)-2 inhibitors, and metalloproteinase and angiogenesis inhibitors may interfere in the stepwise progression of breast tissue from normal to cancerous, regardless of hormone receptor status. In the Royal Marsden Hospital, more than 300 healthy women aged 35–65 years with one first-degree relative with breast cancer have already been randomised in a double-blind trial between an extract of red clover (Promensil, 80 mg of isoflavones) and placebo [31]. Monitoring includes mammographic breast density, endometrial ultrasound, bone mineral density and lipid profile. Different methods in use for non-medical breast cancer prevention were also discussed, but the results are as yet not available [18]. Based on epidemiological links, strategies in normal risk women such as lowering the total intake of fat [27] and daily exercises [28] are unlikely to reduce breast cancer risk substantially whereas reducing alcohol intake may help [29]. The potential of tibolone for prevention of endocrine-dependent malignancies was outlined [33]. Tibolone is a tissue-specific selective oestrogen enzyme modulator (SEEM). It is metabolised to three active compounds that, in a tissue specific way, affect 17ß hydroxysteroid dehydrogenase and sulphatase. In bone, there is a net oestrogen-like effect whereas in the uterus, and in particular in endometrium, the delta 4-metabolite seems to bind the PR and androgen receptor (AR) leading to an anti-oestrogenic effect. In breast, tibolone blocks oestrogen producing enzymes and it increases apoptosis. Studies testing the effect of tibolone on long-term endometrial safety and quality of life in symptomatic postmenopausal women with and without breast cancer are underway.

3. Adjuvant endocrine therapy in breast and gynaecological malignancies

Endocrine treatment is the most important treatment modality in women with ER-positive breast cancer. Compared with tamoxifen, the latest Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview [35] showed an equal effect of adjuvant polychemotherapy on recurrence and death in the age group less than 50 years; greater reductions were seen with tamoxifen in older women. Based on 80000 women, every patient, regardless of her age or tumour stage with an ER-positive breast cancer will benefit from 20 mg of tamoxifen during 5 years; even after 15 years of follow-up there seems to be a 'carry over' effect. That this may also be true for toremifene was suggested by the Finish adjuvant study [36]. They compared toremifene 40 mg with tamoxifen 20 mg during a 3 year period in 1153 ER- and node-positive postmenopausal breast cancer patients showing both compounds to be equally effective after a mean follow-up period of 4.4 years. There were more vascular complications (deep vein thromboses, cerebro-vascular events, and pulmonary embolisms) among tamoxifen-treated patients compared with toremifene-treated patients whereas bone fractures and vaginal leucorrhoea were more common in the toremifene group. The number of subsequent second cancers was similar. Both compounds showed a favourable lipid profile.

In premenopausal women with high risk ER-positive breast cancer, the EBCTCG also showed an advantage for ovarian ablation over no adjuvant therapy. Because chemotherapy exerts a part of its activity through its ablative effect on ovarian function, adjuvant ovarian suppression (luteinising hormone–releasing hormone (LH-RH) analogues, surgery or radio-castration) has been compared with adjuvant chemotherapy in at least six randomised trials. The LH-RH agonist, goserelin, has been tested in 1640 node-positive premenopausal breast cancer patients participating in the ZEBRA-trial (Zoladex Early Breast Cancer Research Association) [37]. Goserelin and cyclophosphamide, methotrexate and 5-fluorouracil (CMF) were found to be equivalent in terms of recurrence-free survival. Amenorrhoea was achieved more rapidly and more completely and was more often reversible with goserelin than with CMF. Side-effects for the two treatment groups were typical for chemotherapy and endocrine therapy, but better accepted by the goserelin-treated group. After 3 years, losses in bone mineral density recovered in the goserelin group whereas losses persisted in the CMF group. Ovarian suppression in combination with tamoxifen even improved relapse-free survival over those treated with classical CMF according to the Austrian Breast Cancer Study Group [38]; the French [39] and the Italian Breast Cancer Adjuvant Study Groups [40] showed a similar beneficial effect of combined adjuvant hormonal therapy compared with anthracycline-based and classical CMF chemotherapy, respectively. From these trials, ovarian suppression plus tamoxifen seem, in a premenopausal setting and for oestrogen sensitive tumours, equivalent to adjuvant CMF or FEC (epirubicin 50 mg/m^2) in terms of efficacy. Polychemotherapy

and hormonaltherapy, however, are not mutually exclusive. In high-risk premenopausal women with ER-positive breast cancer, the combination of ovarian ablation and tamoxifen following anthracycline-containing chemotherapy seems to add to the benefits of anthracycline-containing chemotherapy alone, at least for recurrence-free survival [41] but studies (UKCCR-ABC and IBCSG-VIII) comparing the combination of polychemotherapy and endocrine therapy with endocrine therapy alone are as yet not mature. In postmenopausal women with node- and ER-positive breast cancer, there are some data that this may be so. A small survival benefit (5%) of adding anthracycline-containing chemotherapy to tamoxifen compared with tamoxifen alone has been reported [42]. The authors form this study, at the ASCO-2002 meeting, have also proven that adjuvant tamoxifen should only be started when chemotherapy is completed. Therefore, many consider anthracycline-based chemotherapy combined with endocrine therapy, 5 years of tamoxifen for those in the menopause or ovarian suppression plus tamoxifen for premenopuasal patients, as the 'standard of care' for a high-risk ER-positive breast cancer patient. An adjuvant 'hormonal therapy only' should be chosen for the eligible premenopausal patient who refuses chemotherapy, for the one who is unfit for chemotherapy or for those with a non-high risk ER-positive breast cancer.

It needs to be stressed, however, that survival advantages are small and that not all studies (mainly those using CMF-containing regimens) showed such an overall benefit of combined chemo-hormonal therapy over hormonal therapy. Endocrine treatment modalities may become even better now that the new generation aromatase-inhibitor anastrozole has shown a promising benefit in the adjuvant setting and both anastrozole and letrozole have shown benefit in the neoadjuvant setting. Data from letrozole and exemestane in the adjuvant setting are awaited.

The three armed adjuvant trial, named ATAC (Arimidex, Tamoxifen, Alone or in Combination) [43], compared tamoxifen with anastrozole or the combination in a double blind randomised trial in 9366 postmenopausal women with breast cancer. The preliminary results were formally presented 10 days after the FGOG-meeting at the 2001 San Antonio Breast Cancer Conference. Following a median follow-up of 33.3 months and 1079 events, anastrozole showed superior efficacy to tamoxifen for disease-free survival and incidence of contralateral breast cancer. Anastrozole was better tolerated than tamoxifen apart from musculoskeletal disorders and bone fractures which were more frequently reported in the anastrozole group. These data confirm the already known benefit of the new generation aromatase inhibitors over tamoxifen in achieving a response when used in the neo-adjuvant setting in postmenopausal women with a locally advanced ER-positive breast cancer [44]. At the last ASCO meeting (2002), a panel of experts was convened to analyse whether the latest ATAC data should change standard practise at this time. The panel's conclusion were that data were to preliminary to prescribe aromatase inhibitors in the adjuvant setting and that tamoxifen remains standard adjuvant therapy in ER-positive breast cancer.

Loibl [45] presented the role of adjuvant hormonal therapy following primary treatment of endometrial cancer and concluded that most trials failed to demonstrate a survival benefit of progestins/tamoxifen following treatment for endometrial cancer. As 53 and 80% of endometrial cancers tested positive for ER and PR, respectively, The South Western German Gynaecology Oncology Group randomised 388 patients to receive adjuvant hormonaltherapy following primary therapy for endometrial cancer of either medroxyprogesterone acetate 500 mg daily, tamoxifen 30 mg daily or observation for 2 years. There was a non-significant benefit for those in the tamoxifen arm. As this subgroup has an excellent 5-year survival of $>90\%$, there is currently no benefit from progestins or tamoxifen as an adjuvant therapy after primary surgical treatment for endometrial cancer.

Oestrogen replacement therapy (ERT)/HRT is generally considered to be contraindicated in breast cancer patients as no firm data are yet available from ongoing random-ised trials like the HABITS trial [46]. A large literature overview considered ERT not strictly contraindicated in women treated for early stage endometrial cancer, despite a theoretical risk. We would only consider this option for those suffering from severe menopausal symptoms resistant to alternative treatments after informed consent.

4. SERMs and the uterus

From baseline endometrial findings in 285 patients participating in the endometrial sub protocol in the ATAC study [47], we know that one-fifth has an asymptomatic endometrial lesion in the uterine cavity; polyps and subendometrial fibroids were most frequently encountered. A high incidence of polyps in asymptomatic women on HRT has also been observed by Van den Bosch [48]. The first generation SERM, tamoxifen has been associated with all sorts of endometrial lesions from small to huge glandulo-cystic polyps, polyp cancers, adenomyosis, uterine fibroids, small blue cells in Papanicolaou (PAP) smears, endometrial hyperplasia, endometrial cancers, sarcomas and mixed mesodermal tumours. Although such lesions are present in over three-quarters of long-term tamoxifen users, most, however, are found in sub-epithelial endometrial stroma and caused by glandular cystic atrophy and stromal fibrosis. Van Leeuwen [49] reviewed the total available literature on tamoxifen and endometrial

lesions and showed convincing evidence that tamoxifen is associated with a moderately increased risk of endometrial cancer. The consistent results across these studies, the observed duration response relationship and the well-described oestrogen-agonist effects of tamoxifen on the endometrium strongly support a causal relationship. Tamoxifen for 2 years increases a woman's risk for developing endometrial cancer 2-fold, while use of tamoxifen for 5 or more years produces a 4- to 8-fold excess risk. This risk is dose independent as this side-effect has been described with either dose used in clinical practice in the adjuvant setting (20–40 mg daily). The most recent EBCTCG overview [35] also showed an increased risk for previous users. It remains controversial whether obese women are at increased risk. However, patients with a pre-existing endometrial pathology and those previously using ERT may be at greater risk. Several studies did not find different stage distributions or histological subtypes of endometrial cancers comparing tamoxifen-treated women with those diagnosed and not treated with tamoxifen. Most of these studies considered endometrial cancer cases appearing in the first couple of years on therapy. In the Dutch study, which included 309 patients with endometrial cancer following the diagnosis of breast cancer, van Leeuwen and colleagues reported more advanced stages of endometrial cancers among long-term tamoxifen users than in non-users [49]. Pathology slides were centrally reviewed and those on tamoxifen more often had malignant mixed mesodermal tumours or sarcomas of the uterus; tumours were more often p53-positive and ER-negative and 3-year actuarial endometrial cancer-specific survival was significantly worse for long-term tamoxifen users than for non-users. Other studies have confirmed these findings after long-term tamoxifen use. Despite this excess risk in endometrial cancer, the proven benefit of this drug in controlling breast cancer far outweighs the excess morbidity and mortality due to endometrial cancer. Prompt investigation of gynaecological symptoms is preferred over systematic screening of breast cancer patients. Whether a levonorgestrel-loaded intra-uterine device that induces more bleeding probably due to a decidual endometrial reaction, also protects against tamoxifen-induced polyps and cancers remains unclear [50]. A Scandinavian trial examines the role of the levonorgestrel coil following removal of endometrial polyps and long-term results are awaited. Goldstein [51] set the stage for a new debate on the screening consensus as reported after the first international meeting of the FGOG in 1997 [1]. The effectiveness of endometrial screening has so far not been proven and there is no place for blind endometrial sampling or unenhanced transvaginal ultrasound scanning. Simple ultrasound is, in contrast to sonohysterography, unable to differentiate between sub-epithelial and intracavitary endometrial lesions with a potential malignant behaviour.

Because some patients may be at identifiable high-risk relative to their chance of developing atypical hyperplasia on long-term tamoxifen treatment, baseline screening remains of value, especially in those women with an as yet unproven benefit of tamoxifen as in the prevention setting. In cases of a baseline endometrial polyp or in cases of atypical hyperplasia, the risk of developing endometrial disease on tamoxifen is highly significant. Starting with a normal uterine cavity should not lead to any additional investigation in an asymptomatic tamoxifen user over the first 3 years. Those who need to be screened thereafter, are those with a progressive thickening endometrium of more than 10 mm; hysteroscopy or saline infusion sonography will be able to identify the patient who develops endometrial lesions of clinical significance. Goldstein's conclusion was that baseline screening remains advisable to differentiate between low- and high-risk patients; any research setting testing the value of screening for endometrial lesions in women using a SERM, and maybe also HRT, should take this risk factor into account respecting the consensus as debated before. Studies on the uterine safety of raloxi-fene have not taken this into account because all women had a normal endometrial cavity at baseline. It is, however, unlikely that raloxifene is oestrogenic like tamoxi-fen because endometrial cancer cases have been reported less frequently in long-term raloxifene users. It should, however, be taken into account that the number of cases is low and follow-up is no longer than 5 years with raloxifene. The 6-month data from Euralox 1, a randomised controlled double-blind trial comparing the uterine effects of raloxifene with a continuous combined HRT, a preparation of 2 mg of oestradiol with 1 mg of norethisterone acetate for duration of 12 months were presented [52]. Unlike ccHRT, 6 months of raloxifene treatment does not lead to vaginal bleeding/spotting and is not associated with increased endometrial thickness or uterine volume. Berlière [53] presented data on the endometrium in a small group of tamoxifen-treated women receiving aromatase inhibitors. Sequential use did not lead to thinning of the endometrial layer.

5. Endocrine therapy of advanced and metastatic oestrogen-dependent cancers

Two important issues in the adjuvant therapy of oestrogen-sensitive breast cancer in premenopausal women are also relevant for those in the metastatic setting. It is believed that patients in whom chemotherapy induces amenorrhoea have improved disease-free survival compared with those not becoming amenorrhoeic [54]; however, the type of evaluation biases many of these studies. Time may be crucial, amenorrhoea lasting at least 2 years is more likely to be clinically significant, the

benefit of which can only be assessed in prospective randomised trials. The second milestone is the beneficial effect of combining tamoxifen with oestrogen deprivation. Over 700 Vietnamese breast cancer patients were randomised either to ovarian ablation plus 5 years of tamoxifen or observation only with this treatment modality at first relapse. Initial endocrine therapy led to an improved 5-year disease-free survival (from 54 to 73%) and 5-year overall survival (65–76%) compared with initial observation only [55].

In the metastatic setting, the combination of ovarian suppression with tamoxifen is superior, although there is no significant difference between response rates for each (surgical castration, LH-RH analogues or tamoxifen) treatment alone [56]. Objective response rates increased to 50% with a doubling of the 5-year overall survival to 34%. In addition, a high response rate in patients with ER-positive visceral disease was found in 60% of the patients on combined treatment. For postmenopausal women with advanced breast cancer and failing on tamoxifen, five trials of third generation aromatase inhibitors challenged megestrol acetate and aminogluthetimide as second-line endocrine therapy. More recent trials with these compounds challenge tamoxifen as first-line therapy in women with advanced oestrogen sensitive breast cancer. Exemestane inactivates aromatase by 98% and leads to a further tumour response in patients progressing on megestrol acetate, aminogluthetimide, anastrozole and letrozole. Compared with the first two compounds, time to tumour progression, time to treatment failure and overall survival was better in those on exemestane. Preliminary results of a phase II study comparing first-line exemestane with tamoxifen suggest a 3 times higher response rate for exemestane as well as a longer time to tumour progression in the exemestane arm [57]. Anastrozole has shown significantly superior overall survival and has tolerability benefits versus megestrol acetate in patients progressing on tamoxifen. Two randomised, double-blind trials comparing tamoxifen 20 mg daily and the non-steroidal aromatase inhibitor anastrozole 1 mg daily as first-line therapy for advanced breast carcinoma in postmenopausal women were presented [58]. The combined study population included 1021 postmenopausal women; in a subgroup analysis of ER- and/or PR-positive tumours (60% of combined trial population), anastrozole was superior to tamoxifen with respect to time to progression (median values of 10.7 and 6.4 months for anastrozole and tamoxifen, respectively). Both anastrozole and tamoxifen were well tolerated with fewer venous thrombo-embolic events and vaginal bleeding in the anastrozole-treated group. Data on letrozole's superiority over megestrole acetate in two randomised clinical trials including women with advanced breast cancer and progressive on tamoxifen were also presented [59]. Both trials demonstrated superiority of letrozole over megestrol acetate, but one trial showed an advantage for the 2.5 mg dose over the 0.5 mg dose whereas the other trial showed an advantage of the lower letrozole dose. There was a trend for superiority of the higher dose over the lower dose in a trial of letrozole versus aminogluthetimide; 2.5 mg of letrozole was therefore selected for the first line setting. Compared with tamoxifen, 2.5 mg letrozole demonstrated clear superiority as first-line endocrine therapy for time to progression (9.4 versus 6 months) and overall response rate (32 versus 21%) in a study of 907 postmenopausal women with advanced or metastatic breast cancer; over 40% had visceral involvement [60]. Although there was no overall survival benefit of letrozole in this study, a survival benefit over tamoxifen during the first 24 months was demonstrated; there was no benefit at later timepoints [61]. In postmenopausal women with hormonally-sensitive advanced breast cancer, the new generation of aromatase inhibitors should now be considered as the new standard first-line treatment because of their better tolerability and no apparent loss of overall benefit by changing the sequence (lack of cross-resistance in cross-over data).

The first results of a phase II randomised double-blind study with two dosages of arzoxifene, a new generation SERM and raloxifene analogue, as first-line endocrine therapy in women with metastatic breast cancer were also discussed [62]; three-quarters were oestrogen-sensitive and almost all women were postmenopausal. Response rates of 34% with objective response and stable disease lasting at least 6 months in 64% of cases were reported. A phase III trial in this setting against tamoxifen is ongoing. Similar data are available for arzoxifene in women with metastatic endometrial cancer. Arzoxifene's SERM profile, anti-oestrogenic in uterus and breast, but oestrogenic in maintaining bone density and lowering cholesterol levels holds promises for future trials in the adjuvant and preventive settings.

Vergote presented data on fulvestrant ('Faslodex'), a potent steroidal anti-oestrogen that mediates its effects by a dose-dependent ER/PR downregulation and a more complete blockade of the ER-dependent pathway, in postmenopausal patients with advanced breast cancer progressing after prior endocrine therapy, mainly tamoxifen [63]. Assessing efficacy and safety of fulvestrant 250 mg once monthly with anastrozole 1 mg daily in two phase III trials, he concluded that fulvestrant is at least as effective as anastrozole in second-line advanced breast cancer in women progressing on or after prior tamoxifen. In the North American trial, there was a longer duration of response for fulvestrant compared with anastrozole. Fulvestrant was also well tolerated and is the first anti-oestrogen reported to be at least as effective as a new generation aromatase inhibitor. Furthermore, data were presented showing that there appears to be no significant cross-resistance between fulvestrant and other

endocrine therapies (aromatase inhibitors and progestagens). There are as yet no solid data available on the effects of fulvestrant on lipids and bone. The results of trials, comparing tamoxifen with fulvestrant in first-line metastatic breast cancer will soon be presented.

Howell [64] further alluded to a model showing that ER-positive tamoxifen-resistant breast cancer cells grow through the effect of growth factors other than oestrogens, such as epidermal growth factor and insulin-like growth factors acting through specific receptor tyrosine kinases at the cell surface. This super family of ligand-activated growth factor receptors triggers cascades of biochemical signals that influence tumour cell motility, invasiveness, angiogenesis, and survival, as well as proliferation. The therapeutic utility of blocking these receptors has been established using trastuzumab (Herceptin), a monoclonal antibody that blocks erbB2 signalling and ZD1839 (Iressa), a small molecule which selectively inhibits EGFR-TK. Resistance to tamoxifen is associated with up-regulation of the EGFR-TK pathway and mitogen-activated protein kinase activity is substantially increased in tamoxifen-resistant MCF-7 cells. ZD1839 treatment of tamoxifen-resistant MCF-7 cells blocks mitogen-activated protein kinase activity. Furthermore, treatment of wild-type MCF-7 cells with tamoxifen and ZD1839 prevents development of tamoxifen resistance. These data support the potential clinical utility of ZD1839 in tamoxifen-resistant breast cancer and suggest the possibility of preventing resistance by the early use of combination ZD1839 with anti-oestrogenic agents such as tamoxifen or fulvestrant. The future of breast cancer therapy lies in optimal sequencing of (LH-RH agonists in premenopausal women) tamoxifen, fulvestrant and the aromatase inhibitors probably in combination with monoclonal blockade of selective growth factor receptors [64].

The expression of GnRH and its receptor as part of an autocrine regulatory system of cell proliferation has been demonstrated in a number of human malignant tumours other than the breast, such as ovary and endometrium. The GnRH receptor interacts with the mitogenic signal transduction of growth factor receptors and related oncogene products associated with tyrosine kinase activity, via activation of a phosphotyrosine phosphatase, resulting in downregulation of cancer cell proliferation. Data on the use of tamoxifen and LH-RH agonists in chemotherapy-resistant ovarian cancers were also presented [65]. Response rates and disease stabilisation have been reported, but only in a very few patients. Recently, it was shown that a second GnRH system exists in primates, in endometrial and ovarian cancer cell lines. In the GnRH-II receptor-positive, but GnRH-I receptor-negative ovarian cancer cell line SK-OV-3, native GnRH-II, but not the GnRH-I agonist triptorelin, had antiproliferative effects.

In metastatic endometrial cancer, high doses of progestins led to a response rate of 20% with a figure of 10% being reported for tamoxifen in monotherapy. There may be a theoretical advantage of a sequential combined approach using tamoxifen's oestrogenic effect to induce the PR combined with a progestin, but few such patients have been included in trials. Future trials will test the value of SERMS like arzoxifene, pure anti oestrogens, aromatase inhibitors and anti-progestins for this indication. All have demonstrated anti tumour activity in patients with advanced endometrial cancer, but their clinical role in this setting can only be assessed in phase III trials comparing them against the standard therapy of progestins.

6. Endogenous and exogenous oestrogens and breast cancer

In the postmenopausal woman, body weight, or maybe better, body mass index, is a marker of oestrogenicity. A low fat, high carbohydrate diet leads to lowering of oestrogen and progesterone levels by 20 and 35%, respectively, leading to less dense breasts, as has been seen with an Asian diet [66]. This also explains why breast and bone mineral density are markers for breast cancer risk. According to Fentiman, BMI is a prognostic marker for women with breast cancer through its effect on vascular space invasion [67]. In his own experience, he was able to show how surgery in the luteal phase of the menstrual cycle improves prognosis in both node-positive and node-negative patients with early ER-positive breast cancer; what matters as a protective tool are progesterone levels during breast surgery [68]. This, however, remains a controversial topic and hasn't been confirmed in all well designed prospective studies published more recently [69]. In contrast to other reports, there was one presentation on the protective effect of the progestin, dydrogesterone, which, when added to oestradiol reduces proliferation and increases apoptosis in an *in vitro* model of MCF-7 breast cancer cells [70]. However, this finding doesn't change our current practice to abandon progestins in a hysterectomised woman supplemented with oestrogens. The endometrium of a non-hysterectomised woman exposed to any form of pure oestrogens, whether the dose is moderate or high and probably also with low dose and low potency oestrogens, will always need to be counterbalanced by some form of a progestin, which not only prevents endometrial hyperplasia but also improves adherence to therapy. In the short term, there are enough data that this approach is safe for the endometrium, but with extended duration of use of hormone replacement therapy (perhaps more than 10 years), the relative risk of the development of endometrial cancer begins to increase [71]. Although irregular bleeding is less likely under sequential than continuous therapy, sequential use of HRT is less protective for the endometrium than the continuous combined approach,

but long-term data (> 5 years) are missing [72]. From the recently stopped Women's Health Initiative Study, we now have evidence that conjugated oestrogens in continuous combination with low dose of medroxyprogesterone acetate increase a woman's breast cancer risk with 1 per 1000 per year of use. It was also mentioned by Foidart [46] that not all oestrogens and progestins are used with the same dosage, route of administration (oral, transdermal, intravaginal, intranasal) and that different molecules show a different bioavailability and tissue effect. Available data do not allow discriminating for all these variables per treatment; it would therefore be inappropriate to state that all forms of HRT have the same effect on breast and uterus.

7. What is the profile of the ideal endocrine therapy?

The standards for success of any new SERM to be developed were presented [73]. Its effect on breast cancer, invasive and carcinoma *in situ* clearly needs to be superior to tamoxifen with a proven benefit second-line following development of resistance to tamoxifen. Its risk profile needs to be superior to raloxifene, with a potential for breast cancer prevention and maybe also for benign breast lesions. Evidence should be available that this compound leads to a significant increase in bone mass with protection against osteoporosis and osteroporotic fractures as has been proven for both raloxifene and tamoxifen in the postmenopausal setting. Its oestrogen profile on lipids and vascular health should lead to protection against arteriosclerosis and myocardial infarction. Side-effect profiles will be compared with the existing SERMs raloxifene and tamoxifen and should clearly perform better on central effects like hot flushes and thrombo-embolic risks.

The non-gynaecological, mainly metabolic effects of SERMs and aromatase inhibitors on bone turnover, cardiovascular tissues, lipids, carbohydrates and cerebral function were reviewed [74]. Most of these effects are ER-mediated, but an effect through the recently described 'membrane-bound ER' is not excluded. Raloxifene behaves as an oestrogen on cardiovascular effects. It lowers serum homocysteine levels to a comparable extent with HRT in postmenopausal women. In healthy postmenopausal women, raloxifene, unlike HRT, does not influence cardiovascular risk as predicted by C-reactive protein. The results of ongoing phase III trials of raloxifene in high-risk cardiovascular women are eagerly awaited. Women develop Alzheimer's disease more frequently than man. Oestrogens have long been viewed as a neuroprotective molecule delaying Alzheimer's disease. They reduce secretion of ß-amyloid peptides, a central and unvarying component of Alzheimer's disease pathology protecting neural cells from apoptosis. Whether SERMs are neuroprotective is unknown, but a detrimental effect on cognition is unlikely with so many women-years of follow-up.

Aromatase inhibitors lower oestrogen levels and this may affect bone mass and cardiovascular health. Using these agents in the adjuvant or preventive setting will need bone protection and close monitoring of predictors of cardiovascular health such as cholesterol low-density lipoprotein (LDL) and apolipoprotein B levels. Little is known about the effect of aromatase inhibitors and cognitive function. Brain aromatase appeared neuroprotective in an experimental animal model. Careful evaluation of all-cause morbidity and mortality is necessary to determine long-term risk and to plan trials of aromatase inhibitors in the treatment of breast cancer. This is even more important in the prevention setting where potentially healthy women will be treated.

Finally, the non-uterine gynaecological effects of SERMs were presented [75]. SERMs like levormeloxifene and idoxifene increases the water content of the uterus leading to an increased frequency of urogenital prolapse and urinary incontinence. These side-effects prompted premature closure of trials with these SERMs. Such findings have not been reported with raloxifene. This compound was associated in a recently published study with a 50% reduction in the risk of pelvic floor surgery [76]. Women using raloxifene were also not at increased risk of developing ovarian cancer [77].

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