Review Article

Tamoxifen and endometrial cancer. Is screening necessary? A review of the literature

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Summary

Tamoxifen is a selective oestrogen receptor modulator (SERM) with anti-oestrogenic activity in the breast and oestrogenic effects in various tissues such as the endometrium, bone and cardiovascular territory. As adjuvant hormone therapy, it has a clear beneficial effect in patients with breast cancer, reducing relapses, contralateral breast cancer and mortality. Its most important secondary effect is a greater rate of occurrence of endometrial cancer. Although the risk/benefit ratio is clearly positive, the follow-up on these patients is still an issue. In women with metrorrhagia, it is clear that an endometrial sample must be obtained for histological examination and the best procedure today is hysteroscopic-directed biopsy. Nevertheless, the need to screen asymptomatic patients is not universally accepted. The vaginal ultrasound scan gives a great number of false positives. This entails more aggressive and more expensive procedures such as hysteroscopic-directed biopsy, meaning greater expense and more complications. As a result, the cost/benefit ratio is not very favourable. The rate of occurrence of endometrial cancer in 1,026 tamoxifen-treated patients with breast cancer in our hospital between 1999 and 2001 was 1.25%. Two cases were diagnosed in asymptomatic patients. In this article, we analyse the literature on the need to screen patients on tamoxifen and about the most appropriate diagnostic protocol.

Key words: Tamoxifen; Endometrial cancer; Endometrial effects; Screening.

Introduction

Hormone manipulation has been used in breast cancer treatment since the 1890s, when Beatson [1] first showed that ovarian ablation was useful for reducing tumours in premenopausal women with metastatic disease dissemination. Nevertheless, Schinzinger [2], who defended ovarian ablation before or at the time of mastectomy, was the first to use adjuvant hormonal treatment.

Tamoxifen (TMX) was synthesised in 1960 in Great Britain. Cole *et al.* [3] in 1971 were the first to communicate its efficacy in breast cancer with metastasis. The FDA approved it in 1977. It belongs to the family of selective oestrogen receptor modulators (SERMs). It is currently the most prescribed antineoplastic drug in the world with experience in more than 10 million women [4]. Moreover, it is the endocrine treatment of choice in all stages of breast cancer in pre- and postmenopausal women [5, 6]. Likewise, there are promising data on its efficacy in reducing the rate of occurrence of breast cancer in healthy women at high risk for breast cancer. According to the Breast Cancer Prevention Trial of the National Surgical Adjuvant Breast and Bowel Project, it reduces the rate of occurrence of breast cancer in these women by 45% [7]. It was approved in chemoprevention in the USA in October 1992 [8]. Although the risk/benefit ratio leans towards benefit, over the years evidence has been accumulating of a significant increase in the rate of occurrence of endometrial cancer among patients that use it. The diagnostic strategy to follow for the early detection of premalignant endometrial lesions and endometrial cancer in these patients is not clearly established today.

Mechanism of action

TMX belongs to the family of anti-oestrogens. Anti-oestrogens are compounds that impede the uptake of oestrogens in the target tissues upon bonding with the oestrogen receptor. There are two groups of anti-oestrogens: pure and mixed. The mixed antagonist-agonist action anti-oestrogens include triphenylethylene derivatives (non-steroidal relatives of oestrogens, such as clomiphene and TMX) and non-steroidal agents containing sulphide (benzothiophenes such as raloxiphene).

TMX is very similar to clomiphene in structure and action. Both are non-steroidal compounds related to diethylstilbestrol. TMX binds to oestrogen receptors and competitively inhibits the binding of oestrogens. In vitro, the binding of oestrogens with their receptor is 100-1,000 times greater than that of TMX. Therefore, the concentrations of TMX must be 100-1,000 times greater than that of oestrogens to maintain inhibition of breast cancer cells. In vitro studies indicate that it does not kill the cells, but rather its action is cytostatic (consequently, the treatment must be long-term).

The TMX-receptor complex binds to DNA, thus preventing oestrogens from binding to it. It also acts as a powerful transcription factor on a number of genes, including genes that code the receptor of progesterone and proteins that regulate cell growth [9]. Some of these proteins, when secreted by tumour cells, stimulate growth by binding to receptors of neighbouring cells. The net result of receptor blocking by TMX is reduced tumour growth through detention of the tumour cells in phase G0/G1 of the cell cycle [10]. Whether the oestrogen agonist or anti-oestrogen antagonist action predominates is determined by the promoters present in the specific cell types [9].

Treatment with TMX is more effective when the tumour has hormone receptors. The response is 80% when both receptors (oestrogen and progesterone - ER and PR) are positive, 30-40% when they are positive only for oestrogen (ER+, PR-), 40-45% when they are positive only for progesterone (RP+) and 10% when both are negative. The length of the response varies from 9-18 months [11]. Nevertheless, it is also somewhat effective, although much less, when the tumour does not have ER. This may be due to some of its actions that are not related to binding to the ER. An example is its inhibition of the activity of protein kinase C (phosphorylation). It inhibits the calmodulin-dependent action of cAMP-specific phosphodiesterases by binding to calmodulin. At the same time, the effects of TMX on growth factors are the opposite of those of oestrogens. TMX stimulates the secretion of TGF-b in breast cancer cells, in fibroblasts and in stromal cells, and TGF-b inhibits the growth of cancer cells in the breast. Oestrogens and insulin reduce the secretion of TGF-b in breast cancer cells. TMX reduces the production of IGF-I and IGF-II in the fibroblasts of the stroma, while oestrogens increase it [12]. TMX also inhibits angiogenesis and induces apoptosis [13].

Randomized clinical studies have indicated that there are no convincing reasons for prolonging breast cancer treatment with TMX more than five years. The data even suggest that survival and recurrence rates get worse with more protracted treatment, probably through the appearance of TMX-resistant tumours [14, 15]. There are several theories to explain this resistance. It is believed, however, that a TMX-resistant sub-population is already present from the start and, with time, grows until manifesting clinically [16].

Gynaecological actions of TMX on endometrium

Endometrial cancer

The endometrium is highly sensitive to oestrogens and responds to the weak oestrogen action of TMX with the high, prolonged doses of adjuvant breast cancer treatment. The actual increased risk of endometrial cancer in TMX users has been amply reported since 1985, when Killackey [17] first reported it. Rutqvist *et al.* [18] found an increased risk of 4% in their series, Fisher *et al.* [19] of 7.5% and Curtis *et al.* [20] of 1.6%. The Early Breast Cancer Trialists' Collaborative Group [21] reports an increased risk for the trials of one, two and nearly five years of TMX treatment of 2.2%, 1.8% and 4.2% respectively. This suggests that one or two treatment years with TMX approximately double the rate of occurrence of endometrial cancer (EC) and that five years of this treatment multiplies the rate by four. This rate is very similar to that expected with treatment with unopposed oestrogens [22]. In short the relative risk (RR) of EC is higher in TMX users (RR: 2) than in non-users (RR: 1.2) [23]. A review of 1,026 breast cancer patients treated in our hospital with TMX (20 mg/24 h; mean treatment duration 49.3 months) from January 1999 to May 2001 found the following. The average age of the patients was 66.2 years (47-86). Fifteen neoplasias were diagnosed (1.55%), ten endometrial cancers (1.04%), three ovarian cancers (0.31%) and two carcinosarcomas (0.21%). All the patients but two presented abnormal vaginal haemorrhage. Of these, 70% were moderately differentiated and the remaining 30% were well differentiated. The FIGO stages of the endometrial cancers: two cases were Ia, five were Ib, one was Ic, one was IIb and one was IIIb.

The effects of TMX on the endometrium do not differ in postmenopausal women without breast cancer. In the NSABP P-1, a placebo/control clinical trial of chemoprevention of breast cancer, the risk of EC was 2.5 times higher in women that received TMX [13]. This increased RR is quite modest and only adds two to three extra cases of EC per year per 1,000 TMX users. The risk is related to the total duration of the treatment [13, 23]. Some authors [24] report an additional risk factor for prior users of hormone replacement therapy (HRT).

The concomitant use of progesterone or norethisterone to try to avoid or reverse the endometrial effects of TMX in postmenopausal women has not yet been effective. Neither has its cyclic use [23, 25]. We need more studies to clarify the effect of the progesterone-medicated IUDs [26].

Prognosis

As for the types of EC clinical pathologies diagnosed in these patients, some authors report a more aggressive histological type of worse prognosis [27], but other authors do not find these differences in non TMX-users [19, 20, 23, 28]. In a case-control study, Bergman [29] reports worse prognoses for TMX-treated patients diagnosed with tumours in more advanced stages, with more aggressive histological types (sarcomas and mullerian mixed tumours) and less survival. This author concludes that TMX increases the risk of EC. He observed a poor prognoses in patients with prolonged TMX treatment (> 5 years). The general computation, however, was favourable to the use of TMX in patients with breast cancer, although its chemoprophylaxis function is not so clear in healthy patients. The NSABP P-1 found

an increase in the greater rate of occurrence of uterine sarcomas in TMX-treated patients (12 cases) versus controls (0 cases). They accounted for 10% of the total malignant uterine pathology [30]. All the invasive ECs diagnosed in the Breast Cancer Prevention Trial were in Stage I [19]. Other authors hold that most endometrial cancers occur after a short treatment period with TMX and that what is probably happening is stimulation of the growth of pre-existing cancers [31].

Cystic atrophy of the endometrial mucosa

Atypical endometrial mucosa of patients exposed to TMX has been described. Hysteroscopic observation shows a smooth, whitish, hypervascularised, atrophic endometrial surface with protuberances distributed over the whole surface representing "glandulocystic atrophy" [32]. This type of mucosa is completely different from that of the postmenopausal woman that does not receive TMX. The latter is pale and thin and has no protuberances [33]. The histological characteristics of this glandulocystic atrophy are multiple cystic areas in the atrophic endometrium in a dense, fibrous stroma [34]. The exact location of these cysts is polemical. Some authors place them in the endometrium, while others place them in the myometrium (adenomyosis?) [35, 36]. The presence of these cysts in the endometrial mucosa in TMX-treated patients does not appear to be a premalignant lesion [35].

Endometrial polyps

The rate of occurrence of endometrial polyps in patients that have received treatment with TMX oscillates between 12% and 25% compared to the 4% observed in breast cancer patients that have not received TMX [33, 34]. It is the most common endometrial pathology described in association with TMX exposure. In symptomatic patients (bleeding), the rate of occurrence is between 13.4% and 35.7% [37, 38]. Various risk factors have been reported in postmenopausal patients for developing recurrent endometrial polyps: age, long-lasting breast disease, obesity, echo-thickened endometrium and a history of HRT [39, 40]. Biron-Shental [41] states that there is a group of patients especially sensitive to TMX. This would explain the tendency of some of these patients to develop recurrent endometrial polyps very early. This author holds that the combination of low parity, menopause at a very early age, diagnosis of primary endometrial polyps and a short time on TMX will identify patients with a high risk of developing recurrent endometrial polyps whether treatment with TMX is prolonged or not. TMX-related polyps are different. They are larger (average 5 cm). They are differentiated microscopically by a combination of proliferating activity (glandular cystic dilation), aberrant epithelial differentiation (metaplasia) and focal periglandular stromal condensation. This stromal condensation has been postulated to be related to mullerian mixed tumours [34] and increases the difficulty when they are resected hysteroscopically [33]. Malignant changes have been observed in the polyps with a frequency of 3-10.7% [40] versus 0.5% in healthy women [42]. McCluggage *et al.* [43] report five cases of endometrial cancer in endometrial polyps. Two of them developed in patients on TMX. Beliere [44] reports the case of a benign endometrial polyp resected from a patient receiving adjuvant TMX treatment for three years. Endometrial cancer was diagnosed a year later. This suggests that the resection of benign pathology in patients on TMX does not protect them against subsequent development of malignant pathology. Ismail suggests that the endometrial polyp would be an intermediate stage between simple endometrial hyperplasia and endometrial malignancy [34]. Cohen *et al.* [42], in their series, report 3% malignancy compared to the 0.48% in the controls. They hold that complete hysteroscopic resection of the polyp is imperative, since polyps have been found with small malignant foci.

Endometrial hyperplasia

A significant increase in the rate of occurrence of endometrial hyperplasia has been reported in postmenopausal breast cancer patients on TMX. The rate of occurrence was 1.3%-20% versus 0-10% in the general population [33, 45]. Kedar [46] found a 16% rate of occurrence of atypical hyperplasia. Note that 23% of atypical hyperplasias can progress to carcinoma versus only 2% of those without atypia [45].

Other gynaecological findings

Patients on TMX also presented a greater rate of occurrence of ovarian cysts, growth of pre-existing myomas, adenomyosis and exacerbation of endometriomas or endometriosis de novo, although the latter relationship is not very clear [9, 23, 45]. No signs of malignancy were observed in the myomas that increased in size after TMX [33].

Ovarian cysts

An increase in the rate of occurrence of ovarian cysts has been reported in TMX users. In 1971, Klopper and Hall showed that TMX induces ovulation in anovulators [47] and we must remember that its structure is very similar to clomiphene [9]. In a prospective study, Mourits [23] found ovarian cysts in 40% of 60 premenopausal patients on TMX.

The percentage rose to 81% among the premenopausal patients with regular menstruations. In the latter, the oestrogen and progesterone concentrations were high. The gonadotrophin levels, however, were normal or slightly high, that is, the action of TMX on the ovaries is direct. The aspect of the cysts was benign, unilocular and functional, and only one twisted and required surgical treatment. Therefore, the attitude with these cysts must be conservative. In Kazandi's [48] series of 38 postmenopausal patients treated for breast cancer with adjuvant TMX, five (13.2%) presented ovarian cysts. Three were laparotomised and the histological finding was "simple ovarian cyst".

Menstrual disorders in premenopausal women

In premenopausal patients, TMX alters the cycles. Irregular cycles and oligoamenorrhea or amenorrhea were observed in at least half of them. In these patients, contraceptives (barrier or IUDs) should be used since gestations have been described and TMX can be teratogenic because of its anti-oestrogenic effects on the foetus [23]. The most frequent secondary effects that appear in TMX treatment are abnormal vaginal bleeding, vaginal dryness and hot flushes [4].

In a chemoprevention trial [49], EC presented in patients that were premenopausal and presented amenorrhea during long-term treatment with TMX, with low serum levels of E2. Ultrasound scan of the endometrium showed endometrial thickening.

Other organs

TMX also exerts an oestrogen agonist action in the liver and bone, and an antagonist action in mammary cells. Twenty milligrams of TMX is almost as powerful as 2 mg of estradiol for lowering FSH levels in postmenopausal women [9]. Changes in the serum proteins also reflect TMX's oestrogen action: decrease in antithrombin III, cholesterol and LDL cholesterol. Nevertheless, the levels of HDL and SHBG increase, the same as other binding globulins. The action on triglycerides is variable with a small, but insignificant increment, although some authors have reported marked hypertriglyceridaemia with serious complications [50, 51]. The effects on the cardiovascular system are polemical and apparently conflict. TMX also increases the relative risk of cardiovascular accident (CVA), deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE), while it is associated with a decrease in risk of dying from myocardial infarction [54, 55]. At the experimental level, large doses cause liver cancer in rats, but this has not been described in humans [21]. A beneficial effect on bone has been reported in women with breast cancer as well as healthy women, with a reduction of hip, radius and vertebrae fractures [7]. In postmenopausal women in clinical trials, TMX produced a higher density of the trabecular bone and a reduced tendency for the cortical bone to lose density with a 50% reduction of hip fractures with respect to the control group [52].

A certain ocular toxicity has also been reported, provoking retinopathy and keratopathy, although this is not absolutely clear [53]. What does seem well identified is an increased risk of developing cataracts in women on TMX [7].

Risk/benefit ratio

The main results of the Early Breast Cancer Trialists' Collaborative Group, which includes 55 large randomised trials of adjuvant TMX in women with breast cancer, are the following.

Reductions in breast cancer relapses, mortality and contralateral breast cancer after five years of treatment with TMX were 47%, 26% and 47%, respectively.

The rate of occurrence of endometrial cancer was approximately double in the trials of one or two years with TMX and approximately four-fold in the five-year trials with this drug (odds ratio: 2.2, 1.8 and 4.2, respectively). The absolute reduction in contralateral breast cancer was nearly double the absolute increase in the rate of occurrence of endometrial cancer. It had no apparent effect on the rate of occurrence of colorectal cancer.

We can conclude that the risk-benefit ratio in breast cancer patients as adjuvant treatment is clearly favourable. In women with ER negative tumours, adjuvant TMX treatment is still a problem to be researched. Nevertheless, some years of adjuvant TMX treatment notably improved 10-year survival with reductions in mortality and of breast cancer relapses in women with ER positive tumours and in women whose tumours were not ER classified. Indications for its use as chemoprophylaxis in healthy patients need thorough revision [4, 21, 31, 55].

Diagnostic methods for endometrium surveillance in patients on TMX

Ultrasound scan

Most of the evidence described in the literature on the effects of TMX on the endometrium is based on echographic and/or hysteroscopic images. This is because the changes are subepithelial, which greatly hinders biopsy and usually little or no tissue is obtained for study [4].

The ultrasound scan is the first-line diagnostic procedure for assessing the endometrium. The echographic studies showed that TMX produced an increase in endometrial thickness with a "Swiss cheese" pattern [56]. Histopathological examination macroscopically revealed numerous varied-size intra-endometrial cysts. Microscopically, they corresponded to glandular cystic dilation together with oedema and condensation of the stroma [34]. The pseudo-endometrial thickening appears after the first six months of treatment and gradually progresses with TMX use [57]. The thickening appeared in the first six months of treatment and remained stable for one to three years [58]. This thickening returned to normal after cessation of TMX treatment [59, 60]. Nevertheless, other authors assert that the risk of EC remains after cessation of TMX, the same as the protective effects on the breast. Therefore, surveillance must continue after withdrawing the treatment [29]. The endometrium is no more than 5 mm thick in normal postmenopausal women. In women on HRT, normal endometrial thickness may exceed 8 mm. Endometrial thickness in women on TMX is polemical. In general, the thickness in women on TMX versus those that are not is 9-13 mm vs 4-5.4 mm [33]. An endometrial thickness greater than 5 mm was reported in 41-53% of these patients [61]. Taking a section value of 4-8 mm, the most common echographic pattern was that of a thickened endometrium with cystic areas (Swiss cheese pattern). Lathi *et al.* [39], with a section value of > 5 mm, detected only 51% endometrial pathology. Kedar [46], with an 8-mm section, found 100% PPV. Ciatto *et al.* [62] reports a sensitivity and specificity depending on section values. For > 3 mm, > 4 mm, > 6 mm, > 9 mm, specificity was 25.8, 44.5, 76.1, 91.5% and sensitivity was 100, 91.6, 75, 66.6%, respectively. Gerber [60] proposes a 10-mm section in asymptomatic patients to try to reduce the false positive (FPs) and, consequently, unnecessary aggressive tests. In contrast, Renard and Vosse [63] report an EC in a 64-year-old, asymptomatic patient with operated breast cancer and 55 months of TMX treatment. Her endometrial thickness was 3 mm. Cervical-vaginal cytology detected atypical endometrial cells. Seoud [64] reports another case of EC with an endometrial thickness of 3 mm. In this case, however, the patient presented abnormal vaginal bleeding.

Once the endometrium has thickened, and this occurs in up to 54% (> 5 mm) of patients that receive TMX [60], the sensitivity and the specificity of the ultrasound scan is very poor since the rate of false positives is very high, between 46% [61] and 56% [66]. In patients treated with TMX, the value of the vaginal ultrasound scan lies in the normal findings. It cannot differentiate between a polyp, which may contain a cancer, and endometrial glandulocystic atrophy. These cases require examination with hysterosonography/hysteroscope, since blind biopsy of the endometrium has serious limitations in the screening of this endometrial thickening [13, 45].

Hysterosonography

The use of hysterosonography has improved the capacity of the ultrasound scan to diagnose intrauterine anomalies and to solve any discrepancies between endometrial thickening with vaginal ultrasound scan and little or no endometrial material obtained through needle biopsy for histological diagnosis [56, 67]. Specifically, hysterosonography is associated with vaginal ultrasound scan. It is very useful for defining intrauterine lesions, whether they are pedunculated, and whether they are endometrial or subendometrial [33, 68]. In a study with 114 breast cancer patients on TMX, Tepper [69] reports a 100% specificity for hysterosonography and a 95.5% PPV in those patients that had an endometrial thickness > 8 mm by vaginal ultrasound scan. Hann found 100% sensitivity for hysterosonography compared to 4% for endometrial biopsy in a retrospective study of 51 patients treated with TMX. Consequently, he advises hysterosonography in patients with vaginal bleeding or thickened endometrium with negative endometrial biopsy [70].

Hysteroscope

Hysteroscopy is considered a very useful, powerful diagnostic procedure for identifying endometrial pathology [71, 72]. Its safety is well documented [73]. Oronzo [72] reports 97% safety and 100% specificity in a study that compared the histological results obtained after hysteroscopically-directed biopsy to the histological findings after hysterectomy. It is the only method that provides a direct view of the endometrial cavity and the possibility of performing directed biopsies [45].

Hysteroscopic-directed biopsy in the diagnosis of endometrial cancer in breast-cancer-operated patients with adjuvant TMX treatment is contemplated as a secondary procedure after vaginal ultrasound scan for symptomatic patients (abnormal vaginal bleeding) or patients with a thickened and/or irregular endometrium [72, 74].

Blind endometrial biopsy and curettage

Although needle biopsy has proven to be a safe procedure and useful for diagnosing endometrial cancer in the general population [75], it is not usually a safe procedure for diagnosing TMX-provoked endometrial lesions since they are usually subepithelial. Most of the time, we obtain little material for histopathological study [13] and get many false negatives [76]. Barakat [77] found a 3.2% rate of occurrence of polyps using blind biopsy but 25%-27% with hysterosonography and hysteroscopy. Hann *et al.* [69] diagnosed polyps in 63% of their series with hysterosonography compared to 8% with endometrial biopsy. In contrast, a few authors defend endometrial screening of these patients with endometrial cytology [78].

Neither is cervix dilation and curettage of the endometrial cavity a good procedure to clarify the findings with vaginal ultrasound scan in postmenopausal patients on TMX, because frequently endometrial polyps are not diagnosed and most of the time little material is obtained to be able to confirm endometrial atrophy [39].

Doppler

Eco-Doppler flow studies have been carried out to assess the usefulness of this procedure in the surveillance of women on TMX. The changes found are not specific to endometrial pathology. Some authors, however, have found differences with colour Doppler. Atrophic endometrium is observed as avascular with colour Doppler and endometrial hyperplasia and cancer appear profusely vascularised [79]. Other authors report that TMX induces significant reductions in the impedance of blood flow in endometrial and subendometrial vessels in spite of the presence or absence of endometrial pathology. This can be due to the existence of vasodilation [80]. This probable TMX-provoked increase in vascularisation in the endometrium could hinder the usefulness of power-Doppler for diagnosing endometrial cancer in these patients [81].

Magnetic resonance (MR)

Currently significant differences have not been found in the efficacy of MR and ultrasound scan in the diagnosis of intrauterine anomalies in patients on TMX. Like ultrasound scans, MR is highly sensitive in detecting endometrial pathology but has low specificity [82]. Today, MR is only indicated in patients with a pathological ultrasound scan and cervical stenosis that rules out hysterosonography and hysteroscopy, or in those centres that do not have hysteroscopy [33].

Is screening necessary?

The discussion about the necessity of endometrial screening of TMX-treated patients is still highly controversial today. It is very clear in both Europe and the USA that postmenopausal patients treated with TMX and presenting abnormal vaginal bleeding, independently of the results of the ultrasound scan, should have a hysteroscopic examination plus directed biopsy [64]. Nevertheless, there is much less agreement about the course to follow in asymptomatic patients. Many researchers [13, 23, 40, 62, 63, 72, 83, 84] consider these patients a high-risk group and hold that transvaginal ultrasound scan (TVS) is an appropriate procedure for the screening, while other researchers do not consider it necessary [60, 66, 85]. The latter authors assert that the apparent increase in endometrial thickening can be explained by oedema and dilation of the endometrial glands with condensation of periglandular stroma and myometrium, with the remaining epithelium completely atrophic, all of this provoked by TMX. This echographic image justifies the great many false positives, between 46-56% [45, 66], that this diagnostic procedure presents, which entails an increase in aggressive examinations and the consequential increase in cost and complications. Gerber and Fung Kee [60, 66] have observed an increase between 1.4% and 1.7% in the complications in these patients after curettage due to oedema and atrophy of the endometrium. These authors relate that they had to perform 1,265 vaginal ultrasound scans to detect one endometrial cancer (Ib-FIGO), while another two cancers in the same stage were detected by bleeding. In a cost-benefit analysis of the screening of TMX-treated patients, Barakat [85] reports a decrease in mortality of 0.03%. The screening cost is very high in this population. In the USA, the recommendations of the American College of Obstetricians and Gynecologists [86] in asymptomatic, breast cancer operated patients on TMX do not advise screening with ultrasound scan, just a pelvic examination and cervical-vaginal cytology. They warn general practitioners that endometrial cancer is more frequent in these patients and leave the decision to follow-up to the individual gynaecologist. They recommend a histological study when the patient presents clinical symptoms (bleeding). Other authors [44, 83] recommend a study prior to TMX treatment. Berliere, in a series of 575 cases with pretreatment screening, proceeded differently with patients in which no pathology was found and those with pathology (polyps, atypical hyperplasia). In the group with no initial pathology, the rate of occurrence of polyps and hyperplasia was 12.9% and 0.7% and, in the group with initial pathology, 17.6% and 11.7%, respectively. Other authors use the progesterone test to check whether the endometrium is stimulated by TMX [87].

Neven and Vergote [13], following the agreements of the consensus meeting on TMX and uterus (Brussels, 1997), advises a study of the endometrium with vaginal ultrasound scan in asymptomatic postmenopausal patients. If the endometrial line is regular and its thickness is less than 5 mm, the attitude is to wait and observe. If the endometrial line exceeds 5 mm or is irregular, the indication is hysterosonography and/or hysteroscopy plus directed biopsy. Based on prior studies [24], these patients with an atrophic endometrium prior to treatment will probably develop atypical hyperplasia or EC in the three years following the beginning of the treatment with TMX. The yearly follow-up resumes with a vaginal ultrasound scan starting in the third year. The pattern and endometrial thickness are assessed. If it is regular and its thickness is less than 5 mm, the attitude is to wait and observe. If it is greater than 5 mm or irregular, the indication is hysterosonography and/or hysteroscopy with directed biopsy.

We believe that this is the appropriate protocol in the following cases:

– All patients on TMX as chemoprevention, to improve the risk/benefit ratio, since it is lower in these patients than in those receiving adjuvant TMX.

– A second clear indication would be long-term users of TMX because it has been shown that women with pre-existing benign endometrial pathology have a higher rate of occurrence of TMX-related endometrial pathology (polyps, atypical hyperplasia and EC).

– The ultrasound scan of these patients will allow us to detect other gynaecological pathologies such as myomas, adenomyosis, endometriomas or ovarian pathology. Although this may be irrelevant at the time, it can be influenced by the treatment with TMX and, once diagnosed, should be controlled.

– Patients on long-term HRT present a special problem since they will have a thickened endometrium.

We can conclude that the cost/efficacy ratio of endometrial screening of TMX-treated patients is not favourable, although a high-risk subgroup of these patients can benefit from this screening.

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