

LOW DOSE TAMOXIFEN AS TREATMENT OF BENIGN BREAST PROLIFERATIVE LESIONS

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Abstract

The presence of oestrogen receptors in breast structures defining benign lesions, enlightens the opportunity of using tamoxifen for this pathology. Tamoxifen is a selective oestrogen receptor modulator (SERM) with tissue-specific activities: it acts as an anti-oestrogen (inhibiting agent) in the mammary tissue, but as an oestrogen (stimulating agent) on the cholesterol metabolism, bone density, and cell proliferation in the endometrium and thus may be characterized as a mixed agonist/antagonist.

Our study started from the observation that adapting doses for less dramatic breast pathology may significantly reduce the number and incidence of side effects, while remaining effective for the treatment and prevention of recurrent benign breast diseases and, probably, breast cancer [15, 17].

The results of our study suggest that low doses of tamoxifen may be prescribed for benign breast pathology expecting excellent results, especially for proliferative lesions (hyperplasia) and adenosis, associated with a very low rate of side effects incidence.

Rezumat

Prezența receptorilor estrogenici în structura formațiunilor benigne ale sânului oferă oportunitatea de a folosi tamoxifenul pentru a trata această patologie. Tamoxifenul este un modulator selectiv al receptorilor estrogenului cu activități specifice în funcție de țesutul țintă: acționează ca un anti-estrogen (agent de inhibare) în țesutul mamar, și ca un estrogen (agent de stimulare) pentru metabolismul colesterolului, densitatea oaselor și proliferarea celulelor endometriale, putând fi astfel caracterizat drept un agonist/antagonist mixt.

Studiul nostru a pornit de la premiza că adaptarea dozei în funcție de patologia mamară, poate reduce semnificativ numărul și incidența efectelor secundare, rămânând în același timp eficient pentru tratarea și prevenirea bolilor recurente benigne de sân și, probabil, pentru cancerul de sân [15, 17].

Rezultatele studiului nostru sugerează că doze mici de tamoxifen pot fi prescrise pentru patologia benignă de sân, cu rezultate excelente, mai ales pentru leziunile proliferative (hiperplazie) și de adenoză, asociind o rată foarte scăzută de incidență a efectelor secundare.

Keywords: breast benign proliferative lesions, tamoxifen, oestrogen

Introduction

Tamoxifen, as selective oestrogen receptor modulator (SERM), has an obvious role in the treatment and recurrence prevention for positive oestrogen receptors breast carcinomas in both sexes. In the last decade, its indication became clear for breast cancer chemoprevention in patients at high carcinogenic risk [1, 4, 8].

Other uses, such as therapy for premature puberty in McCune-Albright syndrome, premature stop of growth, infertility by lack of ovulation, angiogenesis in lymphangiomas, retroperitoneal

fibrosis and Riedel thyroiditis are not scientifically proven [2, 9]. Meanwhile, the presence of oestrogen receptors in breast structures defining benign lesions (gynaecomastia included), enlightens the opportunity of using tamoxifen for this pathology, as shown in the early 80's by Cupceancu [3].

On the other hand, lots of side effects, some of them very noxious, restrained its use in benign breast's pathology treatment, due to disadvantages overwhelming the benefits.

Our study started from the observation that adapting doses for less dramatic breast pathology

may significantly reduce the number and incidence of side effects, while remaining effective for treatment and prevention of recurrent benign breast diseases and, probably, breast cancer [15, 17].

Tamoxifen is a SERM with tissue-specific activities: acts as an anti-oestrogen (inhibiting agent) in the mammary tissue, but as an oestrogen (stimulating agent) in cholesterol metabolism, bone density, and cell proliferation in the endometrium and thus may be characterized as a mixed agonist/antagonist.

Tamoxifen itself is a prodrug, metabolized in the liver by the cytochrome P450 isoform CYP2D6 and CYP3A4 into active metabolites such as 4-hydroxytamoxifen and N-desmethyl-4-hydroxytamoxifen (endoxifen) which have 30-100 times more affinity for the oestrogen receptor than tamoxifen itself [6]. These active metabolites compete with oestrogen in the body for binding to the oestrogen receptor. In breast tissue, 4-hydroxytamoxifen acts as an oestrogen receptor antagonist because transcription of oestrogen-responsive genes is inhibited, through nuclear chromatin blocking by the endoxifen-receptor complex after its nuclear translocation. The terminal elimination half-life of approximately 5 to 7 days and an estimated half-life of N-desmethyl tamoxifen of 14 days are strong arguments for the treatment with low doses in benign breast pathology. On the other hand, we must count on a delay of therapeutic answer onset of 4 to 10 weeks, because steady-state concentrations for tamoxifen are achieved in 4 weeks, while steady-state concentrations for N-desmethyl tamoxifen are achieved in 8 weeks [10].

Materials and Methods

Benign breast pathology was divided by Dupont and Page in non-proliferative, typical and atypical proliferative lesions, with an associated relative risk of carcinogenesis of 1.0, 1.2 to 2.5, respectively of 2.5 to 4 [7, 13, 14]. We considered that the nature of the breast lesions may be assessed by a proper sonoelastographic technique, so we assessed the sonoelastographic features of the breast in order to include patients in the trial. Data in the literature and personal observations suggested a strong correlation rate (88 to 96%) of ductal oriented Doppler sonoelastography and bioptic findings [11, 16, 19, 20].

A Hitachi EUB-6500 ultrasonograph with a 96 mm transducer of 7.5-12.5 MHz and sonoelastography module cropped data allowing the admittance of 168 out of the 687 breast pathology patients who presented between January 2010 and December 2011 at the Elite Clinic Bucharest. The design of the study was approved by the ethics committee of

the Elite Clinic Bucharest. All patients signed an informed consent and were informed about the option of exiting the study at any time. Clinical and sonographical follow-up was performed at least 24 months after discontinuing the treatment.

All patients with clinical or paraclinical suspicion of malignancy were excluded from the study. The including criteria were the presence of (multiple) proliferative aspects on sonoelastography (122 cases), severe mastalgia (43), failure to previous traditional therapy (local progesterone, *agnus castus*, evening primrose, well fitted brassiere wearing) of at least 6 months (76 cases). Some of the trial's patients had more than one of the above including criteria. We considered epithelial proliferation circumscribed polycyclic hypoechogenicities, hypoechoic thickening lining a lactiferous duct or isoechoic papillary intraductal or intracystic lesions, all of them elastographically scored 3 by Ueno (Tsukuba) and classified as BI-RADS 3 lesions and requiring shorter time observation (3 to 6 months) [16, 20]. Meanwhile, we defined severe mastalgia as intense pain of subjective score of more than 6/10, prolonged for more than 3 days monthly and inducing some social impairment for the patient. For these patients we prescribed for 6 months, 2.5 mg of tamoxifen orally in the first 10 days of menstrual cycle or 10 days per month in postmenopausal patients. In cases of severe mastalgia we allowed the intake of nonsteroidal anti-inflammatory drugs asking the patient to record their use. All patients were instructed to abort treatment in case of menstrual cycle delays and positive pregnancy testing.

All the patients were clinically and sonographically assessed after 6 months. After that only the patients with prolonged symptoms or proliferative breast lesions on echography were closely monitored after another 6 month, as the asymptomatic patients or with non-proliferative lesions on echography were reevaluated after 1 year. We questioned the patients about any discomfort or symptom during the treatment and also the changes in pain intensity and duration, whenever mastalgia was associated.

Results and Discussion

The adherence to treatment was unexpectedly excellent with no abandon recorded. This was certainly due to the detailed discussion with the patients about the principle of modulation rather than inhibition, the importance of reducing the doses to obtain a consistent decrease of side effects and the positive response rate after treatment. For most patients symptomatology was alleviated after 4 to 10 weeks of treatment. One hundred forty seven patients (87.5%) were asymptomatic after 6 months of tamoxifen and, with the exception of 3

patients (1.78%); mastalgia was alleviated for the rest of the group. The proliferative lesions were

undetectable in 87 patients after 6 months (Table I) and in 98 patients after 12 months of treatment.

Table I

Morphological response regarding types of lesions and global lesional response

Lesion type/Response	Total	Scarse (0-25%)	Fair (25-75%)	Good (75-100%)
(lobular) adenosis	42	2	1	39
(ductal) hyperplasia	39	3	3	33
(fibro)adenomas	18	9	6	3
fibrocystic changes	137	16	85	36
solitary cysts	12	8	3	1
fibrosis	88	69	15	4
Patients treated 6 months	168	21	60	87
Patients treated 12 months	21	-	10	11

Among the 147 fair and good responders 142 (96.6% of them or 84.5% of the trial) were still asymptomatic after 6 months (136 representing

92.5% with minor lesions), but just 33% were symptom free (21% with minor lesions) after 24 months (see Table II).

Table II

After treatment symptom free/minor lesions rates reported to the 147 fair/good responders

Time from treatment initiation (months)	Symptom free	Minor lesions
6	142 (96.6%)	136 (92.5%)
12	129 (87.8%)	109 (74.1%)
18	91 (61.9%)	66 (44.9%)
24	48 (32.6%)	29 (19.7%)

No major side effects were encountered in the trial and none of the patients had to discontinue the tamoxifen intake. This included no evidence of thromboembolic disorders, nor endometrial proliferation on pelvic ultrasound. Some mild side effects were registered in 9 patients (5.35%), such as menstrual disorders in 4 patients, minimal episode of vaginal bleeding (1 case), vulvar itching (1 patient), nausea and epigastric pain (2 cases) and dyslipidaemia (increase of triglycerides – 1 case).

Core needle biopsy was recommended and performed in 24 (14.3%) patients, confirming benign breast solid lesions (ductal or lobular hyperplasia, adenoma, simple or sclerotizing adenosis), but the after treatment evolution observed in ductal oriented breast sonoelastography led to only one delayed post-therapeutic biopsy, in one of the few non responsive patients. That patient developed 18 months after the 12 months of treatment a triple negative cancer, revealed at 7.8 mms of size, without positive lymph nodes, which underwent breast conservative surgery with axillar dissection and radiation therapy.

Oestrogen receptors are expressed on benign as well as malignant breast lesions. This fact entitled Cupceanu to use tamoxifen to treat for 2 or 3 months by 20mg of tamoxifen *per* day also benign conditions of the breast in the early 80's with an alleviation of mastalgia in 97% patients [3].

The 1998 NSABP P-I trial included 13,388 women determined by the Gail model to be at high risk for developing breast cancer [8, 13]. The mean follow-up was 54.6 months. All pathology reports of breast

biopsies performed during the study were collected prospectively. The relative risk between tamoxifen and *placebo* groups was individually evaluated for each histological diagnosis. The study stated that tamoxifen reduces the incidence of invasive breast cancer and also the incidence of ductal carcinoma *in situ* and lobular carcinoma *in situ* in high risk patients by about 50%. On the other hand, Randomized IBIS Trial I advocates a 1/3 decrease of incidence of invasive oestrogen receptor breast cancer in women treated 5 years with tamoxifen and Royal Marsden pilot study is sustaining its benefits in preventing breast cancer [5, 13]. These data were explained as results of an effective treatment for some premalignant lesions as well as for subclinical cancers in the opinion of Tan-Chiu [18]. But this enlightened the idea of tamoxifen effectiveness on other benign lesions of the breast than premalignant conditions so the collected data was analysed in order to evaluate treatment's efficacy on benign breast pathology. Special attention is given to the development of biosensors, such as MUC1 protein, that can be used as point-of-care devices to select the target population [2].

4-hydroxi-tamoxifen may be used as topic treatment for chronic mastalgia as an approved US patent delivered on the name of Bruno de Lignieres, connected to the Besins Laboratories, France [PCT/EP2003] [22].

Oestrogen binding to the oestrogen receptor stimulates proliferation of mammary cells with the increase in cell division and deoxyribonucleic acid (DNA) replication, leading to mutations [12]. It was

observed that tamoxifen therapy significantly decreases the overall incidence of benign breast disease (by 28%) and the need for diagnostic breast biopsy [18]. The NSABP P-I study reported the reduction of resulted in statistically significant reductions in the risk of adenosis, cyst, duct ectasia, fibrocystic disease, hyperplasia and metaplasia [18]. The tamoxifen effect on biopsies was most obvious for women undergoing multiple biopsies and for premenopausal women, in whom the number of biopsies was reduced by 35% [8, 13].

The treatment's side effects are well known from the oncological practice and care must be taken even if they are usually rare and subsequently diminished by adjusting the dose. They concern gynaecological pathology (endometrial hyperplasia and cancer, ovarian cysts, menstrual disorders, vaginal bleeding, vaginal bleeding); the skin (flushes, erythema, oily skin, *calvitia*); the sight (corneal opacities, retina lesions, optic neuritis); digestion (nausea, epigastric pain); metabolism (hypertriglyceridemia, episodic hypercalcemia, dysproteinemia); blood (moderate thrombocytopenia, decrease of white blood cells count, thromboembolism), cognitive disorders and others.

In order to avoid the important side effects such as thrombo-embolism and endometrial hyperplasia or adenocarcinoma we tailored the doses for a benign condition and observed excellent results in 84.5% of treated patients with only gentle discomfort for few of them (5.35%). Best achievement of the low-dose tamoxifen therapy was for the hyperplastic lesions and adenosis, representing higher risk features and being usually low rate responders to medical treatment. No biopsy was needed after the tamoxifen treatment in our study, except one case which underwent surgery for a triple negative breast cancer. The results were similar to those reported by Lanzeroni et al [15].

As selective oestrogen receptor modulator (SERM), tamoxifen has also positive effects, by improving bone matrix strength, lowering cholesterol level and reducing breast density by more than 10%, thus making mammography a more sensitive test.

Conclusions

Low doses of tamoxifen may be prescribed for benign breast pathology expecting excellent results and treatment compliance, while decreasing the rate of invasive diagnostic procedures. Tamoxifen's efficacy specially concerns proliferative lesions (hyperplasia) and adenosis. A low rate of side effects and no complications were associated to the low dose tamoxifen therapy for benign breast conditions.

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