Antiestrogenic therapy in breast cancer and endometrial modifications

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Summary

The aim of this retrospective study was to detect endometrial lesions in tamoxifen breast cancer users (menopausal state related). The meaning of genital bleeding during the treatment and the actual incidence of benign and malignant pathology of the endometrium related to length of treatment was also evaluated.

Tamoxifen (TMX) is a nonsteroidal triphenylene derivate with clear antiestrogenic properties on the breast which is used as adjuvant treatment for breast cancer; potential adverse effects include endometrial lesions. Three hundred and sixty-six breast cancer patients were enrolled in this study; 292 patients were treated with 20 mg/daily of TMX as adjuvant therapy and the remaining 74 did not receive therapy. All patients were subdivided in premenopausal and postmenopausal, asymptomatic and symptomatic groups.

All patients underwent ultrasound scans (to examine endometrial thickness) and hysteroscopic examinations before treatment and after one, three and five years. Endometrial biopsy under direct hysteroscopic vision was systematically performed. The pathological histology reports were classified under polyps, simple hyperplasia, complex hyperplasia, atypical hyperplasia, and carcinoma. A higher incidence of endometrial pathology was found only in symptomatic postmenopausal TMX treated patients (27.2% vs 19.5%) between the third and fifth year of treatment.

Key words: Tamoxifen; Endometrial pathology; Breast cancer.

Introduction

In biofeedback mechanisms between oncogenes and gene suppressors, the definition of the roles between growth factors and target cells is fundamental. The most important mechanism of coordination between producers and receptors is represented by hormones [1].

It has also been noted that independently from the oncogenes, hormones can themselves represent factors of tumor growth as can be seen in the interaction between estrogens and the epithelium of the mammary glands [2, 3].

It has also been observed that adequate hormonal stimulation can represent in itself an oncogenic factor owing to increased mutations that activate oncogenes or deactivate oncosuppressor genes [1].

Tamoxifen (TMX), as in the case of most anti-hormones, has estrogenic agonist/antagonist activity according to the target tissues and exposure time.

In many clinical works [4, 5] where TMX was given for a predetermined period in a pre-established doses, it has proved capable of improving disease-free time and overall survival in women with primary and recurrent breast cancer. These effects have been reported in premenopausal and postmenopausal patients [6, 7].

Following this clinical evidence, the use of TMX has recently been extended as a chemopreventive agent in healthy women with a high risk of developing breast cancer [8].

Opposing TMX is the fact that its estrogen agonistic properties induce proliferative activity on the endometrium: this effect increases the expression of VEGF but not of the proto-oncogenes; for other authors the proto-oncogenes increase [9].

This evidence has brought about a large series of clinical studies which have reported a greater incidence of benign and malignant pathologies of the endometrium in women treated with TMX. This risk has been attributed to duration of treatment and rarely to the given doses [10-15].

Moreover, it should be noted that the conclusions of these contributions are not univocal: others examined eight trials on the use of TMX in metastatic carcinomas of the endometrium showing an average regression of the same in 22% of the cases [16-18].

Materials and Methods

The aim of our study was to retrospectively monitor women treated with TMX:

– Macro- and microscopic modifications of the endometrium correlated both with their pre- and postmenopausal state and the length of treatment.

– The meaning of the appearance of genital bleeding during the treatment

– The actual incidence of benign and malignant pathology of the endometrium compared with length of treatment.

With this aim, we analyzed the clinical data of 366 breast cancer patients between 1992 and 1998 and followed for a period of at least five years.

Two hundred and ninety-two patients were treated with 20 mg/daily of TMX for 60 months (12 patients prolonged the treatment up to 72 to 84 months); 74 of the 366 patients had no antiestrogenic therapy and formed the control group.

The two groups were subdivided according to their pre- or postmenopausal conditions (Table 1).

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Table 1. — *Clinical data of breast cancer patients undergoing hysteroscopic evaluation with biopsy between 1992 and 1998.*

	No. of cases	Premenopausal	Postmenopausal
Tamoxifen group	292 (79.8%)	123 (42.1%)	169 (57.9%)
Control group	74 (20.2%)	41 (55.4%)	33 (44.6%)
Total	366	164	202

Table 2. — *Characteristics of TMX treated patients (premenopausal).*

	Tamoxifen	No.	Mean	SD	t	p value
Age	No	41	46.27	4.637		
	Yes	123	46.34	3.938	–.098	N.S.
Menarche	No	41	12.29	1.806		
	Yes	123	12.37	1.548	–.251	N.S.
Body mass index	No	41	25.1534	1.53428		
	Yes	123	25.1174	2.34639	–.092	N.S.

SD = Standard deviation; N.S. = non significant.

All the patients under examination were compared for age, age of menarche, and body mass index.

No statistically significant differences between the two groups were noted (Table 3).

The state of hormonal receptors, with an evident prevalence of positive receptors in the TMX treated group compared to the group with no treatment, is reported in Table 4.

All the patient underwent ultrasound scan (to examine endometrial thickness) and hysteroscopic examination to evaluate the status of the endometrium before treatment and after one, three and five years.

Endometrial biopsy under direct hysteroscopic vision was systematically performed. The pathological histology reports were classified under polyps, simple hyperplasia, complex hyperplasia, atypical hyperplasia, and carcinoma.

Table 3. — *Characteristics of TMX treated patients (postmenopausal).*

	Tamoxifen	No.	Mean	SD	t	p value
Age	No	33	57.73	7.847	–.116	N.S.
	Yes	169	57.59	5.734		
Menarche	No	33	12.55	1.348	–.966	N.S.
	Yes	169	12.24	1.699		
Body mass index	No	33	25.8382	1.14140	–.031	N.S.
	Yes	169	25.8248	2.30256		

SD = Standard deviation; N.S. = non significant.

Table 4. — *Estrogen receptor status.*

Premenopausal			Total
Estrogen receptor status	Tamoxifen		
	Not treated	Treated	
ER+	9/31 (29%)	105/109 (96.3%)	114
ER–	22/31 (71%)	4/109 (3.7%)	26
Unknown	10/41 (24.4%)	14/123 (11.4%)	24
Total	41	123	164
Postmenopausal			**Total**
Estrogen receptor status	Tamoxifen		
	Not treated	Treated	
ER+	9/11 (81.8%)	154/161 (95.6%)	163
ER–	2/11 (18.2%)	7/161 (4.4%)	9
Unknown	22/33 (66.7%)	8/169 (4.7%)	30
Total	33	169	202

Results

Endometrial pathology between the TMX treated group and control group was compared in relation to the menopausal state: the incidence of benign pathology was not statistically significant in either group. On the contrary, a dissimilar incidence between simple and atypical hyperplasia, 6.5% in the group treated with TMX versus 2.4% in the control group, was found with no evidence of increase in the occurrence of endometrial carcinoma (Table 5).

Table 5. — *Histopathological findings of endometrial biopsy (pre-menopausal).*

	Tamoxifen		p value
	Not treated (41)	*Treated (123)*	
Normal or hyp-oatrophic endometrium	30 (73.2%)	104 (84.6%)	N.S.
Polyps	3 (7.3%)	5 (4.1%)	N.S.
Simplex hyperplasia	7 (17.1%)	8 (6.5%)	N.S.
Complex hyperplasia	1 (2.4%)	3 (2.4%)	N.S.
Atypical hyperplasia	0	2 (1.6%)	N.S.
Endometrial cancer	0	1 (0.8%)	N.S.
Total pathology	11 (26.8%)	19 (15.4%)	N.S.

N.S. = non significant.

However, if the histopathological data are submitted to significant statistical testing, no differences between the treated group and the control group result.

In Tables 6 and 7 the incidence of uterine bleeding is compared between the group treated with TMX and the control group. As can be seen in Table 7 (related to menopausal status), 19.5% of the TMX treated group were symptomatic compared to 24% of the non-treated group.

Table 6. — *Histopathological findings of endometrial biopsy (postmenopausal).*

	Tamoxifen		p value
	Not treated (33)	*Treated (169)*	
Normal or hypo-atrophic endometrium	28 (84.8%)	125 (74%)	N.S.
Polyps	2 (6.1%)	13 (7.7%)	N.S.
Simplex hyperplasia	2 (6.1%)	15 (5.3%)	N.S.
Complex hyperplasia	0	9 (5.3%)	N.S.
Athypical hyperplasia	0	5 (3%)	N.S.
Endometrial cancer	1 (3%)	2 (1.2%)	N.S.
Total pathology	5 (15.2%)	44 (26%)	N.S.

N.S. = non significant.

Table 7. — *Histopathological findings in premenopausal asymptomatic un treated patients and TMX treated for breast cancer.*

	Tamoxifen		p value
	Not treated (31)	*Treated (99)*	
Normal or hypo-atrophic endometrium	26 (63.4%)	93 (75.6%)	N.S.
Polyps	1 (2.4%)	2 (1.6%)	N.S.
Simplex hyperplasia	4 (9.8%)	3 (2.4%)	N.S.
Complex hyperplasia	0	1 (0.8%)	N.S.
Athypical hyperplasia	0	0	–
Endometrial cancer	0	0	–
Total pathology	31 (75.6%)	99 (80.5%)	N.S.

N.S. = non significant.

The fact that there were no cases of endometrial carcinoma or complex hyperplasia in asymptomatic patients seems interesting. On the contrary, in postmenopausal patients the incidence of symptomatic patients was 27.2% in the group treated with TMX versus 15% in the control group. Moreover, in these two groups no case of carcinoma was reported and only one case of complex hyperplasia among asymptomatic patients was noted.

It seems noteworthy that, overall, in about 10% of patients suffering from bleeding, no cases of endometrial pathology were found.

In Table 8 the endometrial histopathologic findings at one, three and five years in TMX treated cases are reported. In the premenopausal group there was no evidence of change in pathology after one, three and five years of therapy (global pathology 15.4%). The opposite was seen in the postmenopausal treated group which showed an increase in endometrial pathology in relation to length of treatment and global incidence: 26%.

The differences between the two groups are statistically significant: in particular, all the cases of endometrial carcinoma and atypical hyperplasia are seen between the third and fifth year of treatment.

Table 10 summarizes the cumulative pathology related to the pre- and postmenopausal TMX treated patients. Overall pathology of the patients treated with TMX in postmenopause shows a considerable increase between the third and fifth year of therapy.

Table 8. — *Histopathological findings in symptomatic postmenopausal untreated patients and TMX treated for breast cancer.*

	Tamoxifen		p value
	Not treated (31)	*Treated (99)*	
Normal or hypo-atrophic endometrium	4 (9.7%)	11 (8.9%)	N.S.
Polyps	2 (4.9%)	3 (2.4%)	N.S.
Simplex hyperplasia	3 (7.3%)	5 (4.1%)	N.S.
Complex hyperplasia	1 (2.4%)	2 (1.6%)	N.S.
Atypical hyperplasia	0	2 (1.6%)	N.S.
Endometrial cancer	0	1 (0.8%)	N.S.
Total pathology	10 (24.4%)	24 (19.5%)	N.S.

N.S. = non significant.

Table 9. — *Histopathological findings in asymptomatic postmenopausal untreated patients and TMX treated for breast cancer.*

	Tamoxifen		p value
	Not treated	*Treated (24)*	
Normal or hypo-atrophic endometrium	26 (78.7%)	104 (61.5%)	N.S.
Polyps	2 (6.1%)	6 (3.6%)	N.S.
Simplex hyperplasia	0	9 (5.3%)	N.S.
Complex hyperplasia	0	3 (1.8%)	N.S.
Atypical hyperplasia	0	1 (0.6%)	N.S.
Endometrial cancer	0	0	–
Total pathology	28 (84.8%)	123 (72%)	N.S.

N.S. = non significant.

Table 10. — *Histopathological findings in symptomatic postmenopausal untreated patients and TMX treated for breast cancer.*

	Tamoxifen		p value
	Not treated (33)	*Treated (24)*	
Normal or hypo-atrophic endometrium	2 (6.1%)	21 (12.4%)	N.S.
Polyps	0	7 (4.1%)	N.S.
Simplex hyperplasia	2 (6.1%)	6 (3.6%)	N.S.
Complex hyperplasia	0	6 (3.6%)	N.S.
Atypical hyperplasia	0	4 (2.4%)	N.S.
Endometrial cancer	1 (3%)	2 (1%)	–
Total pathology	5 (15.2%)	46 (27.2%)	N.S.

N.S. = non significant.

Table 11. — *Histopathologic findings and duration of tamoxifen treatment in 292 cases.*

Premenopausal: 123	Postmenopausal: 169					
Duration of treatment (years)	1	2	5	1	3	5
Polyps	4	1	0	5	6	2
Simplex hyperplasia	2	5	1	4	2	9
Complex hyperplasia	1	0	2	0	2	7
Atypical hyperplasia	0	0	2	0	1	4
Endometrial cancer	7	6	6	9	11	24
Total cumulative pathology	19 (15.4%)			44 (26%)		

Table 12. — *Histopathologic findings and duration of tamoxifen treatment in 292 cases.*

Duration of treatment (years)	1	3	5	Total
Cumulative pathology in the premenopausal tamoxifen group (123 patients)	7 (5.6%)	6 (4.9%)	6 (4.9%)	19 (15.4%)
Cumulative pathology in the postmenopausal tamoxifen group (169 patients)	9 (5.3%)	11 (6.5%)	24 (14.2%)	44 (26%)
Total	16 (5.5%)	17 (5.8%)	30 (10.3%)	63 (21.6%)

Discussion

TMX like most hormones has agonistic/antagonistic estrogenic properties (according to the target tissues). These effects have been repeatedly referred to in a large series of clinical studies linked essentially to the duration of drug treatment and to dose administered.

TMX has proved capable of increasing disease-free time and overall survival of pre- and post-menopausal women with primitive or recurrent breast cancer [3].

The use of TMX at prophylactic doses (5 mg/daily) has recently been extended with a chemopreventive function to healthy women with a high risk of developing breast cancer [9].

On the other hand, TMX in its agonistic estrogenic function, induces proliferative activity of the endometrium. This evidence has determined a large series of clinical studies which report globally and specifically increased endometrial pathology in patients treated with TMX; this risk has been clearly correlated to the length of treatment with the drug and not to the given doses [4].

It should also be noted that different clinical studies have reported mixed results [7].

Most authors agree that a transvaginal ultrasound scan represents the best method to reveal eventual endometrial abnormality and to measure its thickness in postmenopausal TMX untreated patients. Many authors recommend a cut-off value for double layer endometrial thickness of 4-5 mm.

Instead, unfortunately, in patients treated with TMX, with the use of transvaginal ultrasound a frequent growth in thickness and other endometrial abnormalities are reported with a variance between the results of ultrasound and those of hysteroscopy of 45-90% [7-13].

In our study, in postmenopausal treated patients, the absence of symptoms (uterine bleeding) is correlated to a low incidence of premalignant findings (1 case of atypical hyperplasia: 0.6%, and 3 cases of complex hyperplasia: 1.8%). The incidence of pathologies found in this group suggests that transvaginal ultrasound should be the first exam carried out followed by hysteroscopic investigation only in cases in which endometrial pathological findings have been evidenced under ultrasonographic examination.

With reference to the same group – postmenopausal patients treated with TMX (symptomatic) – a higher incidence of endometrial pathology was found (endometrial cancer: 1.0%, atypical hyperplasia: 2.4%, complex hyperplasia: 3.6%).

Conclusions

Our results suggest that the risk of endometrial pathology in postmenopausal TMX patients treated increases with duration of treatment, especially between the third and fifth year.

In general, it can be said that in TMX users there is no statistical evidence of increased risk of endometrial cancer in premenopausal women and only low statistical evidence of increased risk of global pathology.

The information gathered by our study might be helpful in the selection of groups of patients, symptomatic or asymptomatic, to undergo repeated hysteroscopic examinations with directed biopsy in pre- and postmenopause conditions.

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