Hysteroscopic follow-up in Tamoxifen treatment for breast cancer

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Summary: In the postmenopausal women endocrinotherapy proves to be as useful as the cytotoxic treatment in breast cancer therapy, regarding the percentage and duration of response, both in prophylactic and palliative therapy, with the advantage of milder side-effects and a better quality of life.

This study was carried out in order to evaluate the Tamoxifen weak estrogenic activity, which could appear during long-term therapies, determining endometrial morphological modifications.

Twenty-one postmenopausal women suffering from breast cancer underwent hysteroscopy with target biopsy or curettage at the same time with mastectomy and afterwards during additional Tamoxifen treatment at 12 and 24 months. Our results confirm that this simple, outpatient endoscopic investigation should be provided as a routine in the follow-up of oncologic patients during hormonotherapy.

Key words: Breast cancer; Hysteroscopy; Tamoxifen.

INTRODUCTION

In 1973, the introduction of Tamoxifen as an antiestrogen constituted a new approach in breast cancer treatment, and in almost twenty years of world experience this drug has proved its effectiveness, close to that of the substances already available. Actually it is the most used single drug in breast cancer treatment.

It is well known that in the postmenopausal age, endocrinotherapy proves to be as useful as the cytotoxic treatment, regarding the percentage and duration of the responses, both in prophylactic and palliative therapy, with the great advantage of milder side effects and a better quality of life ([1, 2, 3, 4]).

Tamoxifen is able to carry out an antiestrogenic effect because of its capacity to compete the estrogens at the receptorial level, in target tissues ([5, 6, 7]). But it is well known too that Tamoxifen also presents an agonistic estrogenic property which, even if weak, during long-term treatment may induce important morphological changes in target tissues (such as endometrium) ([8, 9, 10]).

In fact, Tamoxifen activates the estrogenic receptors, incompletely determining a biological reaction weaker than that deriving from the development of the normal estrogen-receptor complex; in any case this stimulation, even if weak, is stronger than the physiological estrogenic one in menopausal women. Moreover, the direct action on Tamoxifen receptors may have a eutrophic effect. The presence of these receptors at myometrial level could

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explain the frequency of leiomyomas among menopausal women. Finally, some Tamoxifen metabolites have a continuous, pure agonistic action, so their activating receptorial effect is much stronger than that of the original substance.

In relation to the age of the patients, the endometrium generally presents atrophic aspects, but some Authors also describe proliferative and hyperplastic patterns, verified by cytology, hysteroscopic examination and ultrasonography ([11, 12, 13]).

This study was carried out in order to recognise, by hysteroscopy and target biopsy, eventual endometrial modification, in breast cancer patients, treated long-term with Tamoxifen.

MATERIALS AND METHODS

Twenty one women suffering from breast cancer, all postmenopaused for at least one year (average age 63 years) underwent hysteroscopy and target biopsy and eventual curettage of the uterine cavity, contemporarily with mastectomy. Subsequently, following the histologic examination and the hormonal receptor assay, both in the breast and in the endometrium, and additional Tamoxifen treatment (30 ng/day) was foreseen in all patients, for a period going from a minimum of 12 months to a maximum of 2 years. The hysteroscopic follow-up was perfor med in all 21 patients 12-24 months later by a Hamou II hysteroscope, both in simple sedation and in general anaesthesia when tight stenosis of the cervix was present. All hysteroscopic findings were filmed or photographed and, if any changes in comparison with the pre-Tamoxifen treatment endometrial pattern were observed, a target biopsy was carried out.

RESULTS

All 21 patients studied underwent hysteroscopic follow up after 12 months and 17 of them also after 24 months. Seventeen patients presented a prevalently atrophic endometrial aspect before the administration of Tamoxifen, not modified after the treatment. Two patients with endometrial polyps (diagnosed before uterine curettage) showed an atrophic endometrial status after 2 years. The last two cases had been characterized before the treatment with Tamoxifen by local adenomatous endometrial hyperplasia (one case) and by simple endometrial hyperplasia(in the other case). The hysteroscopy at 12 and 24 months showed an endometrial atrophy in the first case, while in the second case the simple endometrial hyperplasia became adenomatous, already after the first year of therapy, remaining still the same even at the 24 months hysteroscopic control (Table 1).

Both these patients had undergone uterine curettage when mastectomy was performed. In all cases analysed there was a constant uniformity between hysteroscopic and histological diagnosis.

Table 1. – *Hysteroscopy findings before and after 12-24 months of Tamoxifen treatment (30 mg/ daily).*

Case series	Hysteroscopic findings before tx treatment	Hysteroscopic follow-up after 12 months	Hysteroscopic follow-up after 24 months
1	E.A.	E.A.	–
2	E.A.	E.A.	–
3	E.A.	E.A.	–
4	E.A.	E.A.	–
5	E.P.	E.A.	E.A.
6	E.P.	E.A.	E.A.
7	A.E.H.	E.A.	E.A.
8	S.E.H.	A.E.H.	A.E.H.
9	E.A.	E.A.	E.A.
10	E.A.	E.A.	E.A.
11	E.A.	E.A.	E.A.
12	E.A.	E.A.	E.A.
13	E.A.	E.A.	E.A.
14	E.A.	E.A.	E.A.
15	E.A.	E.A.	E.A.
16	EA.	E.A.	E.A.
17	E.A.	E.A.	E.A.
18	E.A.	E.A.	E.A.
19	E.A.	E.A.	E.A.
20	E.A.	E.A.	E.A.
21	E.A.	E.A.	E.A.

E.A.: endom. atrophy; E.P.: endom. polyps; S.E.H.: simple endom. hyperpl; A.E.H.: adenomatous endom. hyperpl.

Table 2. – *Estrogen agonist effects of Tamoxifen on the endometrium. Uncontrolled studies.*

Authors	Daly dose (mg)	Duration of therapy	Endometrial effects
Boccardo (1984)	40	3-5 years	Increased cellularity, mitosis, nuclear dimensions
Gottardis (1988)	–	–	Enhanced growth of human endometrial carcinoma transplanted into atymic mice
Hardell (1988)	40	–	Increased risk of endometrial carcinoma
Atlante (1989)	40-60	2-5 years	4 cases of endometrial carcinoma
Fornander (1989)	40	more than 3 years	Increased risk in women treated with Tx for more than 3 years
Malfetano (1990)	20	2-4 years	7 cases of endometrial carcinoma

CONCLUSIONS

In our experience, even restricted to a low number of cases, Tamoxifen has proved to be a drug practically without important general and local (endometrial) effects; in fact, none of the 21 patients had to stop the therapy because of the side-effects of the drug.

Our results do not confirm the estrogenic activity on the endometrium, described by other Authors, due to the long-term assumption of Tamoxifen, except in those cases which had an evolution from simple to adenomatous endometrial hyperplasia. Much research has recently been undertaken in order to demonstrate the partial agonistic estrogenic effects and the possible role of Tamoxifen in the development of endometrial carcinoma.

It can be seen in Table 2 that uncontrolled case series of endometrial cancer have been reported among women receiving 20-60 ng Tamoxifen daily ([9, 10, 16, 17, 18, 19]). Also the laboratory findings demonstrated an enhanced growth of human endometria carcinoma transplanted to atymic mice treated with Tamoxifen; on the contrary, Tamoxifen has an opposite growth stopping effect on breast cancer cells ([15]).

But if we examine the controlled studies (Table 3) it can be noted that the difference of incidence of endometrial cancer in patients treated for breast cancer with Tamoxifen (dose = 20 mg/day) is not so dramatic: 0.3% vs 1% and in the Stockholm trial (40 mg/day), 1.14% vs 0.2% ([16, 20, 21, 22, 23]). Our purpose was not to introduce a new pathogenetic hypothesis, or new monitoring protocols; however some epidemiological results confirm the higher incidence of endometrial cancer in patients treated with Tamoxifen for breast cancer and the possibility that this type of neoplasia may become a iatrogenic disease must be considered.

The estrogenic effect of Tamoxifen and particularly the proliferative one, on the

Table 3. – *Frequency of endometrial cancer in patients treated with Tamoxifen for breast cancer: controlled case sernes.*

Clinical trial	Daily dose (mg)	Duration of therapy (y)	TX+%	Control %
Stockholm trial (1989)	40	2-5	1,4	0.2
Scottish trial (1987)	20	5	0.3	0.1
N. sab. bp. trial (1989)	20	5	0.3	0.2

endometrial tissue, may depend on the doses and be in relation with the duration of the therapy ([16]).

The period elapsing between the beginning of the drug assumption and the development of endometrial lesions varies between 6 and 36 months of therapy.

We believe it is useful and adequate to perform annual hysteroscopical controls in patients under long-term Tamoxifen therapy.

A close follow-up period (every 6 months) should be reserved only to patients showing endometrial hyperplastic patterns at the first control.

Prospective trials of longer duration on endometrial screening are needed in this group of patients, in order to determine the occurrence of this new primary cancer in women with a breast cancer history.

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