Cytologic endometrial surveillance in tamoxifen-treated women

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Summary

The authors report the results of a study conducted on 136 patients affected by breast cancer under treatment with tamoxifen at a daily dose of 20 mg who underwent a strict follow-up including endometrial surveillance. The cytologic evaluation of the endometrium was performed on smears obtained by the endocyte sampling. The results were in accordance with what is reported in the literature. Forty cases presented with hyperplasia which was atypical in two cases. Only in one case did histology show a well differentiated adenocarcinoma. In 25 cases the endometrium resulted to be proliferative in accordance with the effect of tamoxifen, while the remaining 67 cases were atrophic. The investigation was not possible in four cases due to stenosis. In our study the endocyte sampler resulted to be an economic, simple and painless cytologic device, suitable for clinical use because of its low incidence of false positives.

Key words: Tamoxifen; Endocyte sampling; Hyperplasia; Adenocarcinoma.

Introduction

Breast cancer is today the leading cause of death among women and it is clear that most of these cancers are estrogen-dependent for growth and progression.

Many studies have been conducted on therapies to reduce serum estrogen levels or to block the effects of this hormone on cancer cells.

Various attempts of endocrine treatment with antiestrogenic effects have been performed since 1938.

Tamoxifen, synthesised in 1966, inhibits estrogen-induced cell growth by competitive blockage of the estrogen receptor. Because of the drug's efficacy in preventing the progression of metastatic disease and the lack of toxicity, tamoxifen was approved in 1986 for adjuvant treatment in early stage disease [2].

Tamoxifen has a complex action based on: 1) competitive antiestrogenic effects; 2) inhibition of growth factors like TGF-alfa; 3) induction of antiproliferative factors like TGF-beta and finally, 4) direct cytostatic activity to neoplastic cells. However, tamoxifen is not a pure antiestrogen because it also has estrogenic activity, more evident in postmenopause, and it is able to bind specific "receptors for antiestrogen" recently identified.

Various studies have shown a protective effect of tamoxifen in women at high risk for breast cancer expanding the indications of the drug already taken worldwide by millions of women affected by breast cancer. While acting as an estrogen antagonist in the breast, tamoxifen reduces mortality for breast cancer and the occurrence of contralateral breast cancer, it can also have estrogenic effects on the endometrium thus increasing the incidence of endometrial pathology. In fact five years of tamoxifen administration after the diagnosis of breast cancer results in a 50% reduction in the incidence of contralateral cancer, also confirmed by the N.S.A.B.P.* study on chemoprevention of breast cancer. This reduction is maintained for five years after therapy is discontinued [1, 11].

There is much debate about the risks and benefits of tamoxifen, specifically about the incidence of associated endometrial cancer. Many techniques for screening patients have been suggested in order to diagnose precociously an eventual endometrial alteration. The best way to evaluate the effect of tamoxifen on the endometrium is to study the uterine cavity prior to the beginning of treatment and at regular intervals thereafter. When considering which technique should be employed to screen women without symptoms of endometrial origin, who are receiving this treatment, transvaginal sonography, saline infusion sonography, hysteroscopy and cytology are considered the most applicable. The aim of this paper was to show the validity of endometrial cytology as the first diagnostic approach in asymptomatic users of tamoxifen [3, 5, 6, 8, 12].

Material and methods

We conducted our study on 136 users of tamoxifen selected in a series of 600 women affected by breast cancer who underwent surgery in the 2nd Department of Obstetrics and Gynecology after a diagnosis performed at the Service of Breast Diseases of Rome University "La Sapienza" in the years 1990-2000. These 136 patients underwent different types of surgery according to the characteristics of their pathology; 106 underwent quadrantectomy with lymphadenectomy, 25 radical mastectomy and five tumorectomy. Chemotherapy was indicated in ten cases alone, and in 25 cases associated with radiotherapy. The histologic finding was predominantly the ductal

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infiltrating type. Receptors for estrogen were positive in all cases. All the patients in treatment with tamoxifen at a daily dose of 20 mg for at least five years underwent regular and strict follow-up including endometrial surveillance. This latter was performed yearly also after tamoxifen disruption. The evaluation of the endometrium was performed by endocyte sampling considering the positive cost-benefit outcome in mainly asymptomatic cases; only five patients reported abnormal uterine bleeding. Endometrial cytology was obtained by endocyte sampling and smeared directly on slides for fixation and staining: the smears were more difficult to assess than cervicovaginal smears due to the presence of blood and the small size and density of cells. The investigation was not possible in four cases due to stenosis and no inadequate smear was observed.

Endometrial cytology is a relatively safe, efficient and well-tolerated procedure [18, 19, 20].

Results

The results were satisfactory and in accordance with what has been reported in the literature [5, 8, 14]. Forty cases presented hyperplasia which was atypical in two cases and confirmed by hysteroscopy with consequent hysterectomy and oophorectomy. Only in one case did the final histology show a well differentiated adenocarcinoma four and half years after treatment disruption. Nineteen of the 38 cases of simple hyperplasia presented a concomitant ultrasonic image of endometrial pathology and underwent hysteroscopy with target biopsy. Only in six cases out of the 19 above-mentioned were simple or multiple polyps found and treated by hysteroscopic resection with final histology negative for neoplastic pathology. In the remaining 13 cases of simple hyperplasia no endocavitary neoformation was found at hysteroscopy with a histologic finding of low-risk hyperplasia. In 25 cases the endometrium resulted to be proliferative – which is quite in accordance with the effect of tamoxifen on the endometrium – while in the remaining 67 cases the endometrium was atrophic. In the evaluation of the results we found it interesting to take into consideration the time period of tamoxifen treatment. We observed that patients in therapy up to three years presented normal (proliferative) endometrium, while the patients on long-term treatment (more than three years) presented a modification of the endometrial pattern.

No correlation was observed between endometrial pathology and histologic breast findings [4, 9, 13, 14, 15].

Discussion

Analogs of estrogens have been known to be both agonist-antagonist estrogens which suggests a possible relationship between this treatment in patients with breast cancer and endometrial carcinoma. Tamoxifen might act on the endometrium as an estrogen-receptor agonist. However, estrogen-related endometrial carcinomas are usually early stage and low grade, thus the benefits on breast cancer are higher than the risks [10, 17]. Endometrial malignancies can be classified in two major subtypes. The first is associated with excessive exposure both from endogenous and exogenous sources. The second is not related to estrogen exposure and includes clear cell carcinomas (CCC), uterine papillary serous carinomas (UPSC) and other poor prognostic histologic types. Usually the first type occurs in young women while the second one occurs frequently in older women. Some authors report a relative higher incidence of aggressive endometrial tumors of poor prognosis, not linked to exogenous estrogen intake (UPSC and CCC) [22, 23].

Tamoxifen could affect a pre-existing process such as endometrial glandular hyperplasia. An accurate investigation before beginning treatment is suggested both by ultrasound and cytology in order to diagnose eventual pre-existent pathology. UPSC is often associated with a polyp which is also a typical feature of long-term tamoxifen users. Additional investigations such as hysteroscopy and polypectomy and eventually D&C are needed, also in asymptomatic cases, when a polyp is present. Our series has shown that a current dosage of 20 mg/day for no more than five years is quite safe since only one case of endometrial carcinoma came to our observation. Considering the increased incidence of this pathology in women treated with tamoxifen, a valid screening method for an early diagnosis of endometrial lesions is needed. Ultrasound and hysteroscopy are very reliable techniques in the control of endometrial modifications, allowing pathognomonic features to be seen such as polyps or adenocystic pseudopolyps which are tamoxifen induced [4, 5, 6, 7, 16).

However the rare evolution of these lesions to cancer, the high costs and the invasivity of these methods support our opinion that this technique should be reserved as a second level investigation. In our study cytology for endometrial surveillance resulted in a high diagnostic accuracy. In our experience endometrial cytology, performed yearly during treatment and for three years after tamoxifen disruption, showed a low incidence of false positives (atypical hyperplasia and carcinoma). The cytologic device, the endocyte sampling, is economic, simple and painless and therefore very acceptable to patients and suitable for clinical use. We therefore suggest endometrial cytology in yearly follow-up for women treated with tamoxifen. Since endometrial carcinoma is a quite frequent pathology (4th major cause of death for neoplasias in Europe) we think that this procedure could be useful if employed as a screening method for the asymptomatic population over 45 years of age. In symtomatic women histology is preferable [5, 8, 14, 18, 19, 21].

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