Does tamoxifen change oestrogen and progesterone receptor expression in the endometrium and breast?

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Abstract

We studied the expression of oestrogen and progesterone receptors (ER, PR) in postmenopausal women receiving tamoxifen for breast cancer. In addition the literature addressing the question of ER and PR expression in breast tissue during treatment with tamoxifen was reviewed. We demonstrated consistent expression of ER and PR in endometria from patients receiving tamoxifen, with a trend towards a higher proportion of receptor positive specimens during tamoxifen. In breast cancer tissue, the ER content seemed to be reduced following tamoxifen treatment. After short time exposure to tamoxifen, the PR appeared to be increased, longer treatment caused the PR to go down to pretreatment levels or below.

Keywords: Tamoxifen; Endometrium; Breast; Breast neoplasm; Oestrogen receptor; Progesterone receptor

1. Introduction

In contrast to the widespread clinical use of tamoxifen very little is known about the expression of steroid receptors in the potential target tissues breast and endometrium during the treatment with the drug. We studied the presence of oestrogen receptors (ERs) and progesterone receptors (PRs) in women receiving tamoxifen as an adjuvant therapy for breast cancer. We also reviewed studies addressing the effect of tamoxifen on ER and PR expression in the breast as identified in a Medline search using the terms tamoxifen, ER, breast neoplasm or breast as search phrases.

2. Steroid receptor expression in the endometrium during treatment with tamoxifen

In our retrospective analysis, standard immunohistochemical staining of ERs and PRs was performed on paraffin sections from formalin-fixed uterine curettings or hysterectomy specimens from 40 patients, who had received 20–40 mg of tamoxifen daily for a minimum of 3 months. ERs and PRs were detected in the nuclei of glandular cells in 24/24 cases of endometrial atrophy (ER/PR-IRS, 2–12), in 8/8 endometrial polyps (ER-IRS, 6–12; PR-IRS, 4–12), in 4/4 adenomatous endometrial hyperplasias (ER-IRS, 3–8; PR-IRS, 1–12), and in 4/4 well-differentiated endometrioid adenocarcinomas (ER-IRS, 2–12; PR-IRS, 6–8). This was not statistically different from the ER and PR expression in a group of 9 postmenopausal women with atrophic endometria serving as controls. However, it appeared that in the latter we had a larger proportion with endometria showing no ER or PR expression.

Others have seen a reduced ER and unchanged PR expression in the endometria from patients receiving tamoxifen in comparison to untreated controls or women on hormone replacement therapy [1]. Reduced stromal cell staining for ER and increased glandular staining for PR was found in a comparison of endometria and endometrial polyps from tamoxifen treated women to a group of age-matched control patients [2]. A similar effect was seen in a study of endometrial cancers treated with tamoxifen for 7–10 days between diagnostic curettage and subsequent hysterectomy. A significant decrease of ER and an increase of PR was observed [3].

Taking together all available data it appears that there is consistent expression of ER and PR in endometria of women receiving tamoxifen irrespective of the underlying histology. In some studies a significant decrease of ER expression and a significant increase in PR expression was observed. This is in accordance with a potential oestrogenic effect of tamoxifen on the endometrium.

3. Steroid receptor expression in the breast during treatment with tamoxifen

Several studies have investigated the effect of tamoxifen on the receptor expression in malignant breast tumours. The somehow conflicting results of the different studies might be explained by the different duration

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Table 1
Synopsis of studies investigating the behaviour of oestrogen receptor (ER) and progesterone receptor (PR) in breast cancer tissue during treatment with tamoxifen

Tamoxifen duration	ER	PR	Detection method	Tamoxifen dose (mg)	*n*	Author [Ref.]
3 days	n.d.	↑	DCC	40	24	Noguchi [4]
7 days	↓	±	n.a.	30	17	Montoya [5]
7 days	n.d.	↑	DCC	40	22	Noguchi [4]
8 days	↑	↓	FNA EIA	20	10	Noguchi [6]
13 days	n.d.	↑	DCC	20	58	Howell [7]
14 days	n.d.	±	DCC	40	21	Noguchi [4]
21 days	↓	±	Biopsy	30	14	Melchor [8]
21 days	±	±	IHC	20	59	Clarke [9]
21 days	↓	n.d.	Biopsy flow cytometry	20	40	Brotherick [10]
6 wks	↓	↓	FNA IHC	20	32	Bajetta [11]
8 wks	↓	±	EIA	20	11	Lundgren [12]

n.d., not determined; n.a., not available; DCC, dextran coated charcoal; FNA, fine needle aspirates; IHC, immunohistochemistry.

of exposure to tamoxifen and different detection methods for the steroid receptors. Taking these limitations into account it appears that the ER content is decreased following tamoxifen treatment, all but two studies addressing this question supporting that finding. The behaviour of the PR seems more complicated with a biphasic response, an initial increase after tamoxifen exposures for up to 7 days and a decrease or normalisation after longer treatment of up to 8 weeks (Table 1).

The data on possible tamoxifen effects on steroid receptor expression in normal breast tissue are rather limited and inconclusive. A small study found no effect on the PR expression in breast cancer associated normal breast tissue, however, a significant increase in ER positivity of ductal epithelium [13]. The receptor expression was highly variable in both, pre- and postmenopausal women and characterised by large numbers of apparently negative cells. A recent study in ovariectomised macaques showed that after 3 years of tamoxifen there is an induction of ER and PR in the mammary glands of these primates in comparison to untreated controls [14].

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