5. Conclusions

Preliminary data show an increased risk in women with undiagnosed cancer at initial screening. The program was designed for calculating the remote risk for breast cancer, but these data are not available yet. The risk analysis may reduce the cost-price of follow-up, increase the women's motivation to improve some of their risk factors and make her more likely to focus on follow-up mammographic examination and preventive medication. After further refining, the risk profile may contribute to the correct interpretation of mammograms.

Abstract: P9

Determination of tamoxifen and its metabolites in endometrial tissue of long-term treated women

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1. Introduction

The need for large samples (usually recovered from surgical specimens) for chromatographic methods has limited the determination of tamoxifen and its metabolites in human endometrial tissue. Instead, mass spectrometry allows the study of drug distribution even in very small specimens.

2. Objective

We have, therefore, studied 23 postmenopausal breast cancer patients on chronic tamoxifen treatment to measure tamoxifen, N-desmethyltamoxifen (metabolite X), N-didesmethyl-tamoxifen (metabolite Z) and 4-hydroxytamoxifen (metabolite B).

3. Materials and methods

Hysteroscopically-directed endometrial biopsy was taken with microforceps (mean: 2 mg of tissue immediately frozen) together with a sample of blood. Endometrial and serum samples were conveniently processed, homogenated and then analysed with mass spetrometry to measure tamoxifen, N-desmethyltamoxifen (metabolite X), N-didesmethyl-tamoxifen (metabolite Z) and 4-hydroxytamoxifen (metabolite B). Quantitative determinations of tamoxifen and its metabolites were made and expressed as ng per ml of serum or g of endometrial tissue. Endometrial concentrations of tamoxifen and its compounds were also expressed as percentage increase of tissue toward serum concentrations, assuming that 1 ml of serum is equivalent to 1 g of tissue.

4. Results

Metabolite X was by far the most concentrated compound both in serum (mean: 318±158 ng/ml) and in the endometrium (mean: 4240±1642 ng/g) but with a serum/tissue gradient of only a 17-fold increase. B metabolite had the highest gradient (more than 400-fold increase with serum concentration of 7.5±5.3 ng/ml and tissue concentration of 1952±1283 ng/ml). Tamoxifen was less detectable in serum (mean: 102.3±44.8 ng/ml) than X metabolite, and was the least concentrated in tissue (mean: 1887±762 ng/g) with a gradient of 22-fold increase. Z compound had an inter-

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mediate behaviour with serum concentration of 28.8±16.4 ng/ml and endometrium concentration of 2047±1809 ng/g (100-fold increase). Serum and tissue concentrations of all compounds were not linearly correlated with treatment duration. No significant relationship was found between hysteroscopic features and compound concentrations. A highly significant ($P < 0.01$) difference in tamoxifen tissue concentration was found between atrophic and hyperplastic endometrium at biopsy.

5. Conclusions

Congruent with previous studies on rats, tamoxifen and its metabolites are actively concentrated in human endometrial tissue as in other human tissue, but it is unlikely that the avidity of these metabolites for oestrogen receptor could totally explain this active concentration. Increased receptor distribution in hyperplastic endometrium could, on the other hand, account for increased tamoxifen concentrations, and this should be further investigated.

Abstract: P10

Downregulation of oestrogen receptor in advanced breast cancer after lipofection with wild-type (w-t) insulin growth factor binding protein IGFBP-2 cDNA plasmid

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1. Introduction

Development of anti-oestrogen resistance and oestrogen independence in human breast cancer is associated with a reduction in the level of secretion of IGFBP-2 (IGF-1 binding protein), which is an important modulator of IGF-1 action. This may be caused due to mutations in IGFBP-2.

2. Objective

Thus, we believed that and studied whether upregulation of IGFBP-2 would enhance the level of IGFBP-2 synthesis and circumvent anti-oestrogen resistance to breast carcinoma cells.

3. Materials, methods and results

We obtained tamoxifen-resistant breast carcinoma cells from a patient by fine-needle biopsy. Immunocytochemistry (ICC) and polymerase chain reaction (PCR) analysis exhibited inactivated IGFBP-2 due to mutations. Then, we encapsulated wild-type (w-t) IGFBP-2 cDNA plasmid in DRV liposomes and incubated these with breast tumour cells at 37°C for 6 h. ICC and PCR analysis exhibited normal expression of IGFBP-2. Furthermore, electron microscopy exhibited induction of PCD in treated tumour cells. Subsequently, these tumour cells were incubated with tamoxifen-molecules for 4 h at 37°C. Biochemical assays such as DNA synthesis (BrdU) metabolic activity (MTT), clonogenicity and trypan blue viability showed much lower percentage values compared with controls.

4. Conclusion

Gene replacement using liposomal w-t IGFBP-2 cDNA circumvented tamoxifen resistance in advanced breast carcinoma cells.

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