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Third generation aromatase inhibitors and inactivators in the treatment and prevention of breast cancer

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Third generation type I steroidal irreversible aromatase inactivators and type II non-steroidal reversible aromatase inhibitors are, 100 to 1000 times more potent compared with the original non-steroidal aromatase inhibitor aminoglutethimide. They are completely selective and induce seldom, moreover mild to moderate adverse events (hot flushes, nausea, fatigue), and are generally well tolerated by compliant patients. They induce a quite maximal inhibition of aromatisation, a suppression of levels of circulating oestradiol and oestrone beyond the limits of detection, a suppression of levels of circulating oestrone sulphate by more than 90% and an inhibition of the production of oestrogens in ovaries, in normal as well as in cancerous mammary tissue and in other peripheral organs. In second- and third-line hormonal treatment of advanced breast cancer, individual products have been able to demonstrate markedly improved outcomes in comparison to treatment by means of progestins. Individual studies, not only in menopausal but even in younger patients, observed improvements in objective response and overall success rate, in median duration of response and overall success and in median time to progression. In one study in second-line treatment, a statistically significant benefit in terms of overall survival has been demonstrated with exemestane. Use of aromatase inactivators and inhibitors is currently studied also in first-line treatment of advanced breast cancer, in adjuvant and neo-adjuvant approach of early breast cancer, as well as chemoprevention in women at risk. The aromatase inactivators (formestane and exemestane) produce a different pharmacological effect on aromatase within the tumour compared with the aromatase inhibitors (anastrozole, letrozole). Formestane must be administered intramuscularly for optimal biochemical and clinical effects whereas exemestane with a half-life of approximately 24 h, can be administered once daily, orally.

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Expression of oestrogen receptor α (ER α) and β 1 (ER- β 1) in endometrial adenocarcinoma

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1. Introduction

Endometrial adenocarcinoma is generally known to be hormone-dependent. It is dependent both on oestrogens and progestagens. Expression of the classic oestrogen receptor (ER) differs in various patients, but is not connected with their age. After cloning the β form of ER [1] from a rat's prostate, and then from human testis, and after the possibility of the interaction between α - and β -receptors (ERs) — following the stimulation of receptors with 17 β oestradiol — was described, it has become known that α can act as an activator of transcription, and ER β as its inhibitor. All this suggests that the evaluation of ERs expression is of great importance both in aetiology and in the

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assessment of the invasiveness of endometrial cancer. It is also important in treatment which is based on the use of anti-oestrogens.

2. Objective

To evaluate ER expression of type α and β 1 in endometrial cancer in relation to normal endometrium, as well as the evaluation of ER expression in relation to clinical and histopathological parameters.

3. Materials and methods

Samples of control normal endometrium ($n=2$) and endometrial adenocarcinomas obtained during surgical procedures ($n=6$) were immediately frozen at -80°C . RNA was isolated by TRIZOL reagent (GIBCO-BRL) according to the manufacturer's instructions. ER α and β 1 were measured by transcribing the mRNA into cDNA by use of reverse transcriptase (RT), followed by amplification of the cDNA using polymerase chain reaction (PCR). Aliquots of mRNA were transcribed into cDNA by incubating in 20 μl of 10 mM Tris-HCL (pH 8.3), 50 mM KCL, 5 mM MgCl_2 , 1 mM dATP, 1 mM dCTP, 1 mM dTTP, 5 μg oligo(dT)_{18–20}, 20 U RNAsin, 200 U murine moloney leukaemia virus (M-MLV) RT for 30 min at 37°C . The reaction was then heated to 95°C (5 min) and cooled to 4°C . ER cDNAs were amplified using specific primers according to the published sequence.

4. Results

A decrease of ER β 1 expression has been observed in all cases of endometrial cancer, while ER α decreased in undifferentiated tumours (histological degree of differentiation: G2 and G3). In well-differentiated tumours (G1) the ER α type increased.

5. Conclusion

The hormonally-dependent cancerous tissue showed a general lowering of ER expression. An increase in the ER α expression in the earlier (well differentiated) types of endometrial adenocarcinoma can be viewed as a positive prognostic factor. Further studies should indicate whether, in analogy with breast cancer, the increase or the unchanging levels of ERs can be viewed as an indication to treat endometrial adenocarcinoma with SERMs.

Reference

1. Kuiper GG, Enmark E, Peltö-Huikko M, Nilsson S, Gustafsson JA. Cloning of novel receptor expressed in rat prostate and ovary *Proc. Natl. Acad. Sci. USA* 1989, **93**, 5925–5930.

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The presence of (sub)endometrial cysts is not a suspicious sign in postmenopausal patients with breast cancer who are treated with tamoxifen

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