combination of radiotherapy and this compound showed a cytotoxic effect in 87% of an ER-sensitive human breast tumour in nude mice. Clinical studies with these new compounds will help to elucidate if these preclinical effects translate to the desired efficacy in postmenopausal women. The clinical success of currently available SERMs like tamoxifen, toremifene and raloxifene has set the stage for a variety of drug therapies based on the selective modulation of nuclear receptor activity [7].

References

1. McDonnell DP, Clem DL, Hermann T, *et al*. Analysis of ER function *in vitro* reveals three distinct classes of antiestrogens. *Mol Endocrinol* 1995, **9**, 659–669.
2. Mitlak BH, Cohen FJ. Selective estrogen receptor modulators. A look ahead. *Drugs* 1999, **57**, 653–663.
3. Novo Nordisk discontinues osteoporosis development programme of levormeloxifene. *Stock Exchange Announcements* 1998, **20**, 1.
4. He HZ, Paralkar M, Grasser WA, *et al*. Effects of CP-336,156, a new nonsteroidal estrogen agonist/antagonist on bone, serum cholesterol, uterus, and body composition in rat models. *Endocrinology* 1998, **139**, 2068–2076.
5. Sato M, Grese TA, Dodge JA, *et al*. Emerging therapies for the prevention or treatment of postmenopausal osteoporosis. *J Med Chem* 1999, **42**, 1–24.
6. Simard J, Sanchez R, Poirier D, *et al*. Blockade of the stimulatory effect of estrogens, OH-tamoxifen, OH-toremifene, droloxifene and raloxifene on alkaline phasphatase activity by the antiestrogen EM-800 in human endometrial adenocarcinoma Ishikawa cells. *Cancer Res* 1997, **57**, 3494–3497.
7. Couillard S, Gutman M, Labrie F, *et al*. Effect of combined treatment with the pure antiestrogen EM-800 and radiotherapy on the growth of human ZR-75-1 breast cancer xenografts in nude mice. *Cancer Res* 1999, **59**, 4857–4863.

The oestrogen receptor and its selective modulators in gynaecological oncology

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Oestrogens are clearly implicated in the pathogenesis of breast cancer. These hormones are known as potent mammary mitogen substances and are the major stimulus for the growth of hormone-dependent tumours. Endocrine therapy is an active treatment option and in contrast to chemotherapy is effective through selective mechanisms.

1. Receptor and mechanism

Oestrogens and progestins show their cellular effects through the binding and activation of specific nuclear receptors, the oestrogen-receptor (ER) and the progesterone-receptor (PR). Since the original cloning of cDNAs for these receptors, substantial data in the field of steroid hormone action has been obtained.

Molecular studies have shown two different binding sites of the ER protein. At the amino end (TAF1) and at the carboxyl end (TAF2) of the molecule there are independent domains of transcriptional activity. Depending on the relative strength of TAF1 and TAF2 selective oestrogen receptor modulators (SERMs) act as an agonist or as an antagonist. They typically bind to the ER and activate it by forming receptor dimers. The SERM-ER complex binds itself to the DNA binding sites. There are significantly different tissue distributions of the ER leading to different effects of SERMS in different organs.

2. SERMs

SERMs are a new category of therapeutic agents, which bind with high affinity to ERs and mimic the effect of oestrogens in some tissues, but act as oestrogen antagonists in others.

2.1. Tamoxifen

Tamoxifen is a triphenylethylene derivative. As a potent anti-oestrogen compound it has shown its benefit in the adjuvant setting as well as in the treatment of advanced breast cancer. It has oestrogen-like activity on bone metabolism, as well as cholesterol reduction and a reduction in myocardial morbidity. Analysis after 5 years supports the maintenance of decreased low-density lipoprotein (LDL) and total cholesterol. Furthermore, tamoxifen lowers the risk of contralateral breast cancer by 36%. Tamoxifen has been implicated in the development of endometrial tumours in patients.

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0959-8049/00/$ - see front matter
PII: S0959-8049(00)00232-X

2.2. Toremifene

Toremifene is structurally close to tamoxifen. No cases of endometrial cancer have been reported in the marketed use of this compound. Several studies performed in the US and Europe demonstrated at least equivalent response rates compared with tamoxifen in postmenopausal patients with metastatic breast cancer and positive oestrogen receptor status. Toremifene versus tamoxifen is now investigated for the adjuvant setting in postmenopausal patients with positive lymph nodes in Finland. Interim analysis showed toremifene to be at least effective and safe as tamoxifen with less vascular complications.

2.3. Raloxifene

The 2-arylbenzothiophene raloxifene is a SERM which is approved for the prevention and treatment of postmenopausal osteoporosis. Raloxifene is a potent inhibitor of the loss in volumetric bone mineral density and has minimal effects on the endometrium. It was recently approved by the Food and Drug Administration (FDA) for the prevention of osteoporosis in postmenopausal women. Raloxifene therapy reduced the incidence of all new breast cancers by 54% compared with placebo, at a median follow-up of 33 months according to the results of a meta-analysis. This meta-analysis looked at data from nine trials (including MORE) conducted in over 10 000 women. Available data showed no significant differences between raloxifene and placebo in the incidence of endometrial cancer. The most common side-effects were hot flushes, leg cramps venous thromboembolic events.

2.4. Tibolone

Tibolone reduces vasomotor symptoms such as hot flushes and offers benefit with regard to osteoporosis. A significant reduction in high-density lipoprotein (HDL) cholesterol was observed. Tibolone has favourable effects on the fibrinolytic system which may counterbalance the effect on lipoproteins with respect of cardiovascular morbidity. The steroid acts on endometrial tissue as a progestogenic compound.

3. New drugs

3.1. Idoxifene

Idoxifene, a triphenylethylene is currently in phase III testing for osteoporosis prevention and in phase II trials for breast cancer treatment. Idoxifene reduces significantly bone resorption by as much as 25% compared with placebo. The compound also reduces LDL-lipoproteins and lowers serum fibrinogen.

3.2. LY-353381

LY-353381 is a recently developed analogue of raloxifene, which has shown higher antagonistic effects compared with tamoxifen and raloxifene. This compound shows oestrogenic agonist activity in bone and cardiovascular tissues without uterotopic activity in animal models.

3.3. GW-5638

GW-5638 is a newly developed SERM that shows oestrogen-like activities in bone and vascular system with minimal uterotopic activity. In tumour cell lines (MCF-7) this compound has shown comparable effects to tamoxifen in its ability to inhibit the growth of tumour cells.

3.4. Miproxifene (TAT-59)

Miproxifene (TAT-59) has shown anti-oestrogen activity *in vivo* and *in vitro* but effects on other hormonal sensitive tissues have not been investigated.