OLD AND NEW NCE

Before developing new treatments, it may yet be possible to take better advantage of existing ones. An attempt has been made to relate the efficacy of high dose medroxyprogesterone acetate treatment to the bioavailability of this compound which shows large interpatient variations (G. Milano and M. Namer). Instances of the successful use of the potent aromatase inhibitor 4-hydroxy-androstenedione as a second-line treatment of advanced breast cancer patients resistant to the less potent inhibitor aminoglutethimide were described (R. Murray, Melbourne). The possibility that certain progestins may be more effective therapeutic agents than others because they are stronger inhibitors of oestrogen sulphatases was evoked (J.R. Pasqualini, Paris).

The expiration of the patent on the anti-oestrogen tamoxifen, first marketed as Nolvadex® (ICI, U.K.), has led to the proliferation of 10 or so generic formulations in Europe. Research-workers interested in tamoxifen's anti-oestrogen action have meanwhile investigated whether its analogues might not be active on tamoxifen-resistant cells or more suitable drugs as regards toxicity, pharmacokinetics, and so on. This has been indeed reported to be the case for toromifene (a chloro-derivative of tamoxifen) (Farmos, Finland) on sale in Finland. Panomifene (a trifluoro analogue (Egis Pharma, Hungary) and droloxifene (3-hydroxy-tamoxifen) (Klinge-Pharma, Germany) are still in the early phases of clinical development (phases I and II) which focus on safety, pharmacokinetics and dose-finding. In spite of the advantages that could be expected from the presence of reactive halogen substituents or from the direct administration of a hydroxylated compound, it will certainly be some time before the precise clinical role of these compounds will be ascertained.

A follow-up drug to tamoxifen is presently under development by ICI (U.K.). Unlike tamoxifen, the molecule (ICI 182 780) is a steroid and has a long aliphatic side-chain in position C7. Four teams presented results of fundamental research in which ICI 182 780 or its parent compound ICI 164 384 have been used as tools to study the mechanism of anti-oestrogen action. M.G. Parker (London) described how such compounds interfere with the subcellular distribution of the oestrogen receptor (ER) and its turnover. The compounds target ER to the lysosomes where it is rapidly degraded unlike tamoxifen and oestrogen which lead to nuclear localisation of ER. F. Vignon of H. Rochefort's laboratory (Montpellier) demonstrated that these steroid anti-oestrogens, like 4-hydroxy-tamoxifen, block the growth of ER^+-cells by antagonising oestrogen agonist activity but also by preventing the mitogenic activity of growth factors. They do this by either drastically decreasing their high-affinity binding sites and/or by impairing a key event in the transduction of the mitogenic signal. B.S. Katzenellenbogen (Urbana) described a screening system in which anti-oestrogens could be tested on a vast panel of ER mutants for their ability to bind to these receptors and activate their transcription. This work has particular relevance not only to the mapping of the hormone binding site on ER and to an understanding of ER function but also to an appreciation of anti-oestrogen activity on breast tumour specimens rich in ER variants. The fourth presentation (D.L. Manning and R.I. Nicholson, Cardiff) emphasised the superiority of ICI 182780 over tamoxifen in inhibiting MCF_7 cell growth by an action that lowers the viability of these cells and their sensitivity to growth factors and highlighted an unexpected similitude in effect of these steroid anti-oestrogens and the antiprogestin RU 38486. Both these classes of compound are able to induce the mRNA of pBCL1, the first gene to be found to be down-regulated by oestrogen.

Inhibition of malignant cell growth by steroid antiprogestins with bulky substituents in the C11 position such as RU 38486 was first demonstrated by H. Rochefort's team (Montpellier). These initial observations have led to the development of onapristone (Schering AG, Berlin), presently in phase II clinical trials. Besides inhibiting the growth of cell-lines, onapristone is effective after first-line tamoxifen treatment in animal models and would appear to act by using the progesterone receptor to induce differentiation and programmed cell death (H. Michna, Berlin). Like anti-oestrogens, antiprogestins can induce apoptosis.

The 10 year-span needed to develop a NCE could be curtailed by finding original applications for marketed molecules. The art is in solving the equation between substance and clinical application. One such molecule that might find a new outlet in cancer treatment is the anticoagulant polysaccharide pentosan polysulphate. This molecule binds to heparin-binding or fibroblast growth factors produced by breast cancer cells and limits the initiation of tumours in *in vivo* models (M.E. Lippman, Washington). It is presently in phase II clinical trials. Suramin, an antitrypanosomal agent, also inhibits fibroblast growth factor binding to its receptor and reverses the response of this growth factor on Shionogi (S115) mouse breast cancer cells deprived of androgen (J.K. Laine, Turku).

BIOLOGICALS

Much of the recent progress in the development of a variety of biologicals derives from variations on a common tactic: first, identification of proteins that are overexpressed in cancer cells and, second, development of appropriate models to study their regulation and to evaluate potential inhibitors, either NCE or more frequently peptides and monoclonal antibodies. The symposium covered several growth factors, growth factor receptors, proteases, and so on, that are overexpressed in malignant cells but only in a few cases, the insulin-binding growth factor, the epidermal growth factor receptor and some examples below, has the step from basic biological research to investigation of therapeutic applications been taken.

M.E. Lippman's team (Washington) has designed an inhibitory peptide that binds to the fibroblast growth factor site and shows antiangiogenic activity, *in vitro* antiproliferative activity in several cancer cell-lines, and *in vivo* antitumorigenic activity in the nude mouse model.

The HER-2/*neu*, also known as the *erb*B-2 protooncogene, encodes a growth factor receptor with extensive homology with the epidermal growth factor receptor and which is overexpressed in 20–30% of human breast cancers due to gene amplification. Transfection of the gene into human breast cancer and ovarian cells at levels equivalent to human tissue levels leads to increased DNA synthesis, cell growth, and anchorage-independent growth. In nude mice, consistent growth significantly increased by oestrogen is observed. Two teams (D.J. Slamon (Los Angeles) and N. Hynes (Basel)) described work on monoclonal antibodies directed against the extracellular domain of this receptor, several of which suppressed receptor over-expression *in vitro* and delayed the onset of the growth of human tumours transplanted into athymic nude mice. D.J. Slamon observed a 60–80% inhibition according to antibody *in vivo* and an additive or

synergistic effect with *cis*-diamminedichloroplatinum, but not doxorubicin, *in vitro*. Presently, one of his antibodies is in phase 1 clinical trials to assess lack of toxicity in humans and localisation to tumours. N. Hynes has used rDNA technology to produce an immunotoxin. The heavy and light variable domains of one antibody were cloned and a fusion gene coding for a single chain antibody molecule was produced by linking the two domains by a short nucleotide sequence. This fragment was then coupled to a sequence encoding a modified exotoxin A and the whole was expressed in *E. coli*. The immunotoxin thus produced specifically bound to *erb*B-2 protein, inhibited protein synthesis in *erb*B-2 expressing cells and tumour growth in nude mice in a dose-dependent fashion and was considered to have therapeutic potential.

PREVENTION

In view of the real but limited success of existing treatments and the time required for new treatment strategies to get off the ground and enter phase III clinical trials, it is eminently sensible to look at prevention methods that could exploit available medications. Aside dietary fat restriction, several types of drug are reputed to possess a preventive action: tamoxifen, retinoids, oral contraceptives and the progestin gestodene. A retrospective analysis of 10 000 patients included in various tamoxifen trials has shown that there was a one-third reduction in the development of contralateral tumours in the tamoxifen-treated compared to control groups. Such observations and others have led to the setting up of three large-scale trials designed to evaluate the benefits of tamoxifen in prevention. In the trial coordinated by the U.K. and presented by J. Cuzick (London), 15 000–25 000 women will be randomised to receive 20 mg/day for 5 years. Inclusion criteria will be based on the following risk factors: family history (relatedness, age at onset, bilaterality, multiple affected relatives), abnormal pathology (biopsy-proven breast disease except for fibro-adenoma, lobular cancer *in situ*, atypical hyperplasia), nulliparity and mammographic dysplasia.

The use of this type of anti-oestrogen as a preventive measure raised some anxieties. First of all, there have been reports of iatrogenic endometrial cancer but as pointed out by M. Namer (Nice) the estimated benefit afforded by tamoxifen should be weighed against the expected low incidence of endometrial cancer. Fears were also voiced by F. Kuttenn and P. Mauvais-Jarvis (Paris) that, in healthy women, the administration of tamoxifen would lead to polycystic ovaries and high production of oestrogens thus overwhelming the action of the drug. A proposed solution to this problem was a gel formulation of *trans*4-hydroxy-tamoxifen for local administration to the breast.Cell-culture experiments implied that this tactic might be effective and that isomerisation to the *cis*-hydroxy compound would not be a problem.

Concluding remark

As stressed at this symposium on 'Hormones and Breast Cancer—From Biology to the Clinic', the gap between laboratory research and the clinical availability of new treatments is still wide in spite of sustained efforts to improve upon existing drugs, to find new applications for them, to design biologicals on the basis of state-of-the-art knowledge of cellular mechanisms of action, and also in spite of efforts to identify modalities for the prevention of disease in high-risk populations.

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Letters

Follow-up of Breast Cancer patients Stage I–II

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IN THEIR paper Hannisdal *et al.* (992–997) provide further evidence of the lack of efficacy of instrumental tests (chest X-ray, bone X-ray, bone scan) in improving prognosis when used in the periodic follow-up of breast cancer patients. This finding is consistent with other reports comparing the prognosis of asymptomatic and symptomatic recurrent patients and challenges the common and expensive practice of instrumental periodic follow-up.

On the contrary, I do not understand their enthusiam for the use of blood tests as a convenient alternative. According to their results a panel of three tests (alkaline phosphatase, erythrocyte sedimentation rate and glutamyltransferase) had a sensitivity of only 31%. Increasing the sensitivity to 56% would cause the specificity to drop to 91%. Blood tests do not seem to be superior to instrumental tests and the authors provide no evidence that early detection by blood tests may have any favourable impact on prognosis. They also provide no evidence to support the statement that blood tests may be important "to avoid unnecessary morbidity" in recurrent cases. Even admitting such a benefit, someone might argue that the morbidity of earlier treatment of asymptomatic metastases would minimise the final effect on the quality of life.

It seems to me that the paper provides convincing evidence that following up breast cancer patients with blood tests, as well as with instrumental tests, has probably no favourable impact on prognosis. Periodic follow-up should be based on history/physical examination/mammography and diagnostic assessment with blood and instrumental tests should be limited to symptomatic/suspected cases.

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