Parallel Symposia

SY-7. New Developments on Steroid and Other Receptors (September 13)

SY-7-1 Comparison of Technics for ER estimation

S. Thorpe. *Denmark*

Abstract not available.

SY-7-2 Oestrogen Receptor Mutations and Variant Forms

M. Dowsett*, A. Daffada, C. Chan, R. Wooster [1], M. Stratton [1], S.R.D. Johnston. *Dept of Biochemistry, Royal Marsden Hospital, London SW3 6JJ, UK;* [1] *Institute of Cancer Research, Sutton, SM2 5PT, UK*

The oestrogen receptor (ER) is a ligand-activated transcription factor which forms the critical part of the cell's response to circulating oestrogen. Activation occurs by oestradiol binding to the protein with resultant binding of the complex to oestrogen regulatory elements (EREs). While ER probably has fundamental importance in the development of breast cancer (which rarely develops in the absence of oestrogen) it is in the response of established carcinomas to endocrine therapy that most attention has been paid to ER. Nearly all patients that respond to such treatment have ER + ve tumours (ie with > 10 fmol/mg protein). However, at relapse almost all of the patients remain ER + ve. It has therefore been widely hypothesised that ER may be different in relapsed tumours. This could result from mutations (ie changes in the gene structure) or variant forms at the level of mRNA which result from aberrant transcription. Many mutations of ER which have deviant function have been produced artificially and these could, if expressed at high level in a tumour, lead to resistance to oestrogen deprivation and/or increased agonist response to tamoxifen. However, there is little evidence to support their presence in breast cancer. In contrast, a large number of ER mRNA variants have been described in breast carcinomas. The variant lacking exon 5 is found to be constitutively active in some experimental systems. However, this was not significantly overexpressed in our survey of 70 tamoxifen resistant tumours although some evidence for its affecting other phenotypic characteristics was found. The biological and clinical importance of these variants remain to be proven in breast cancer.

SY-7-3 Growth Factor Receptors

J.G.M. Klijn, P.M.J.J. Berns, J.A. Foekens. *Rotterdam Cancer Institute (Dr. Daniel den Hoed Kliniek), Erasmus University Rotterdam, The Netherlands*

An increasing number of growth factors appear to be involved in the malignant transformation, differentiation, proliferation, in different steps of the metastatic process including neo-angiogenesis, and in the development of therapy resistance of tumors. Some of these growth factors or their receptors can be used as a prognostic factor but a valuable prognostic factor for (disease-free) survival can be a poor predictive factor for type of response to therapy and vice versa. Growth factor receptors can be used for: 1) determination of the prognosis of patients with either primary or metastatic breast cancer; 2) selection of (high-risk) patients for therapy; 3) selection of specific type of therapy, depending on patient and tumor characteristics; and 4) development of new treatment modalities directed on growth factors, their receptors and signal transduction. From a therapeutic point of view, overall it may be expected that combination therapies will appear to be most effective because several molecular processes have to be blocked simultaneously in order to prevent that malignant cells are able to escape by different pathways the killing effects of drug therapy. In this presentation an overview on recent data will be discussed.

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SY-7-4 IGF_1, GH an Prolactin Receptors in Human Breast Cancer

J.Ph. Peyrat*, J. Djiane [1], J. Bonneterre. *Centre Oscar Lambret BP 307 59020, Lille, Cédex, France;* [1] *INRA 78350 Jouyen-Josas, France*

Prolactin (PRL), growth hormone (GH) as well as the insulin-like growth factor 1 (IGF1, which mediate the effect of GH), play an important role in the proliferation and the differentiation of the normal animal mammary gland. The role of these hormones in the development of breast cancers is not completely known. *In vitro* experiments have shown that PRL and GH have some effects on breast cancer cells whereas IGF_1 strongly stimulates proliferation. Increases in circulating PRL, GH or IGF_1 have been described in breast cancer patients. Both PRL and hGH recognise lactogenic receptors (PRL/GH-R), which are present, at low concentrations, in 50% of breast cancers. Part of these receptors are masked by endogenous hormones. Recently, we have demonstrated, by RT-PCR and immunohistochemistry, that somatogenic receptors (GH-R) are also present in those tumours. IGF_1 receptors (IGF_1-R) are detected in 90% of the cases. PRL/GH-R and IGF_1-R concentrations are positively correlated to estradiol (ER) and progesterone receptor (PgR) concentrations. PRL/GH-R and IGF_1-R have prognostic value, but it is independent from the prognostic value of ER or PgR. All these results prompted us to initiate, following the ER/tamoxifen model, clinical assays associating bromocriptin (an anti-PRL drug) and somatostatin (an anti-GH and anti-IGF1 drug). The well-described paracrine action of IGF1 and the recent demonstration of the local production of PRL and GH in breast cancer will certainly lead to new anti IGF_1/GH/PRL strategies.

SY-8. New drugs (September 13)

SY-8-1 New Cytotoxic Agents Active in Breast Cancer (BC)

E.A. Eisenhauer. *National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), Queen's University, Kingston, Canada, K7L 3N6*

The past decade has seen the emergence of several new agents of novel mechanism, class or structure with activity in BC. The first of these were the *taxoids* (paclitaxel and docetaxel) both of which act to promote the formation of stable intracelluiar microtubules which leads to cell death. Both agents have shown response rates (RR) in excess of 50% in first-line BC studies and from 25–50% as second-line therapy. Combination regimens with anthracyclines, vinorelbine and other agents are under development. *Camptothecins* produce cytotoxicity through another novel mechanism: inhibition of the DNA enzyme topoisomerase I. Both topotecan and irinotecan, water soluble analogues of camptothecin, have shown evidence of activity in phase II trials in BC (RR from 12–25%). Interestingly, in one study the likelihood of response was related to the level of topoisomerase I in tumour tissue. Further exploration and confirmation of these data are needed. *Gemcitabine* is a cytidine analogue, which unlike ara-C, showed preclinical activity in numerous solid tumour models. It has shown RR of 26% and 46% in two phase II trials in BC and will likely be explored in combination. This presentation will also review other active new BC agents now being studied in randomized studies including *vinorelbine,* a vinca analogue, and *losoxantrone,* an anthrapyrazole compound.

SY-8-2 New Hormonal Agents

R. Paridaens. *Department of Oncology, University Hospital Gasthuisberg, Leuven, Belgium*

One century after the discovery by Beatson that oophorectomy can induce regression of advanced disease, ovarian ablation — which can be achieved by surgical castration, radiotherapy or LHRH agonists — remains the best endocrine treatment for premenopausal patients. In postmenopausal patients, antiestrogenic therapy with Tamoxifen is the modality of choice in first-line. Other non steroidal triphenylethylene derivatives are developed,