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

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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

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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

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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,

without at present demonstration of improved therapeutic efficacy or better therapeutic index. The pure steroidal antiestrogen, ICI 182, 780, is in early phase of testing. Aside Aminoglutethimide (AG), newer non steroidal aromatase inhibitors (NSAI: Vorozole, Letrozole, Anastrozole) achieve a better estrogenic suppression; devoid of significant side-effects, they will supplant AG and progestins in second line. Liarozole, another triazolic NSAI, blocks the intracellular metabolism of retinoids and is currently under phase II testing. The steroidal aromatase inhibitors (Lentaron, Exemestane) irreversibly inactivate the enzyme by covalent binding; they display a weak androgenic activity and are devoid of cross resistance with NSAI. The role of these aromatase inhibitors in earlier line will depend on their effects on endometrial proliferation, lipids, coagulation and bone metabolism.

SY-8-3 New Drugs Other than Chemotherapeutic or Hormonal Agents: The Hope for Innovative Treatment Strategies Against Breast Cancer

M.J. Piccart. *Institut Jules Bordet, Brussels, Belgium*

Our growing knowledge of the molecular biology of breast cancer is beginning to translate into new forms of therapies, with specific molecular targets in the cancer cell. Differentiating agents, monoclonal antibodies directed towards tyrosine-kinase growth factor receptors and antigiogenic-antimetastatic drugs are undergoing clinical evaluation with encouraging preliminary results.

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The new compound liarozole has the unique potential of inhibiting breast cancer growth through aromatase inhibition *and* retinoic acid metabolism blockade. The EORTC-BCCG is conducting a phase II trial in 4 patient subsets characterized by a decreasing probability of response to conventional 2^{d} line endocrine therapy.

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A monoclonal antibody against erbB-2 or Neu has been selected for clinical development in view of its high affinity for the erbB-2 receptor, lack of cross reaction with other receptors, ability to inhibit the growth of a cell line overexpressing Neu, synergism with some cytotoxic agents such as doxorubicin, cisplatin or paclitaxel. Following objective responses in phase II trials, a large phase III study has been launched in Europe and in the US.

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Some specific and potent antiangiogenic and antimetastatic agents are under phase I/II evaluation: updated results on the matrix metalloproteinase inhibitor BB2516 will be presented.

Integration of these new agents into our classical drug armamentarium represents a real challenge to medical oncologists. The hope is that these new agents will be shown to impact on "time to progression" in metastatic disease and will then rapidly move to the adjuvant setting.

SY-8-4 New Bisphosphonates

R.E. Coleman. *YCRC Dept of Clinical Oncology, Weston Park Hospital, Sheffield, England*

The bisphosphonates, in conjunction with standard anticancer treatments, significantly reduce skeletal morbidity from breast cancer, while in about 50% of patients with disease which is refractory to standard therapies useful palliation of pain and improvement in quality of life are seen with intermittent intravenous treatment. Recently, a number of highly potent bisphosphonates have begun clinical testing in the hope that they may provide greater efficacy and/or enable more convenient administration. Ibandronate (BM 21.0955) and Zoledronate (CGP 42446) are of particular interest in oncology. Ibandronate may be given as a 5 minute i.v. injection or by mouth. With the latter, a dose dependent effect on bone resorption is seen with generally acceptable gastrointestinal toxicity at doses up to 50 mg/day. Data from the treatment of hypercalcaemia suggest the duration of action of a single dose is relatively short. Zoledronate may be given as an i.v. bolus while transdermal and subcutaneous formulations are in development. The efficacy of intravenous Zoledronate is being compared with pamidronate for the prevention of skeletal-related events, notably the need for radiotherapy, while intravenous ibandronate is being evaluated in placebo-controlled trials. Their effects on idiopathic and treatment related osteoporosis are also being assessed. Trials to test these compounds as adjuvant therapy to prevent bone metastases cannot realistically be conducted by the pharmaceutical industry alone, and will require a major committment from collaborative groups including the EORTC.

SY-9. Psychological Aspects of Breast Cancer (September 13)

SY-9-1 Patient's Perception

H. Thornton. *UK*

Abstract not available.

SY-9-2 Communication between Breast Cancer Patients and Physicians

L.J. Fallowfield. *CRC, Dept. of Oncology, University College London Medical School, U.K.*

Despite the considerable amount of research published about the psychological consequences of breast cancer, significant numbers of women feel that their information and other psychosocial needs are not met. A lack of information can cause anxiety, uncertainty, distress and dissatisfaction. Furthermore inadequate communication can lead to under-reporting of symptoms and side-effects and poor adherance to treatment regimens. Research shows that women with breast cancer who are dissatisfied with the communication at the time of diagnosis experience more adjustment disorders up to 3 years later than women who were satisfied. Many factors contribute to the problems including inadequate communication skills training. This paper reports an initiative in the U.K. aimed at helping senior oncologists improve their communication skills.

SY-9-3 Quality of Life of Women in EORTC Trials

G.M. Kiebert. *EORTC Quality of Life Unit, Data Centre, Av. Mounier, 1200 Brussels, Belgium*

Despite the fact that important progress has been made in the management of breast cancer, the age-adjusted overall survival of women with breast cancer has not been improved significantly during the past 20 years. This is one of the reasons that quality of life has become an increasingly important endpoint in cancer clinical trials.

The EORTC Breast Cancer Co-operative Group has included quality of life in many of its trials. The first study that included the measurement of some aspects of quality of life was study 10801, a randomised clinical trial for early breast cancer patients comparing radical surgery (mastectomy) versus breast conserving surgery followed by external irradiation as well as iridium implantation. One of the secondary outcomes in this study was to investigate the long term cosmetic results of breast conserving therapy followed by irradiation and the effect this has on their quality of life (in casu body image and fear of recurrence). Since this first study, quality of life has been a secondary endpoint in seven other studies: two in phase II and 5 in phase III studies.

This presentation will provide an overview of the studies that included (aspects of) quality of life as an endpoint and will include some results of the studies that have been analysed.

The EORTC policy and approach to measuring quality of life in cancer clinical trials will be discussed in a broad context as well as the procedures to build on consecutive trials.

SY-9-4 Aspects of Breast Reconstruction

M. Lehman. *France*

Abstract not available.