# Parallel Symposia

## SY-4. Prognostic Factors: Methodology of Evaluation and Impact on Treatment (September 12)

### SY-4-1 Proliferation Markers in Breast Cancers

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The ability to divide subsets of patients with breast cancers into prognostic groups is currently limited. With respect to the determination of proliferation markers in breast cancers, a major problem relies in the confusion which is systematically made between tumour growth and tumour proliferative activity, which are not synonyms. Tumour growth represents the balance between cell gain (number of cells produced per unit of time, i.e. mitoses) and cell loss (number of cell deaths during the same unit of time, for example by apoptosis). Proliferative activity, which can be determined by numerous types of markers (including Ki-67 (or MIB-1), PCNA, S-phase, etc...), relates only to the cell gain compartment. A number of methods are useful in the determination of the cell loss compartment, but are too complex or too tedious to be applied in pathological routines. We therefore developed an original methodology which makes it possible to assess both proliferative activity and cell density (the balance between cell gain and cell loss) in a given breast cancer. Cell density is assessed on Feulgen-stained sections by means of computer-assisted microscopy. Proliferative activity is quantitatively (computer-assisted microscopy) assessed by means of the anti-MIB1 antibody. The relationship between proliferative activity and tissue differentiation was established by quantitatively determining the immunohistochemical amounts of estrogen and progesterone receptors in the series of 20 breast cancers studied here. The present methodology has been validated at the clinical level with respect to sarcomas and astrocytic tumours.

### SY-4-2 Invasiveness Markers

E. Roos. *Division of Cell Biology, The Netherlands Cancer Institute, 121 Plesmanlaan, 1066 CX Amsterdam, The Netherlands*

We have studied adhesion mechanisms in metastasis, hoping to detect molecules that may be used as marker for metastatic capacity. For three carcinoma cell lines, including two variants of the same murine mammary carcinoma, we found that they use three different adhesion molecules to bind to hepatocytes, an important step in the formation of liver metastases. The importance of these molecules was demonstrated with knockout mutants of an embryonal carcinoma, lacking $\beta 1$ integrins, which had a strongly reduced metastatic capacity, in the liver probably because they lack the $\alpha 5\beta 1$ integrin fibronectin receptor.

However, some carcinoma cells express the alternative fibronectin receptor alpha;V$\beta 6$, which may take over this function. We are testing this by expressing $\alpha V\beta 6$ in the mutants. The $\alpha V\beta 6$ integrin is only found in carcinomas and in healing wounds, and may be involved in migration. Also $\alpha 5\beta 1$ is normally not present in epithelial cells, but upregulated in wounds. These are a few examples of the similarities between tumors and wounds, that will be discussed. A systematic comparison may yield additional markers.

### SY-4-3 Cell Surface Mucins in the Biology and Treatment of Breast Cancer

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Cell surface mucins are complex glycoproteins normally expressed on the apical surface of breast epithelium. In malignancy, the MUC-1 gene which encodes polymorphic epithelial mucin (PEM) is upregulated and its apical distribution is lost. Premature sialation of core-region carbohydrates and reduced expression of glucosyl transferases lead to reduced glycosylation of the peptide backbone and consequent exposure of novel peptide and carbohydrate epitopes. Expression of the novel carbohydrate epitope sialyl-Tn (STn), has been noted in ductal carcinoma *in situ* (DCIS) where correlation with grade of DCIS has been noted. In infiltrating carcinoma expression of STn did not correlate with established prognostic features though expression was associated with a poor prognosis and appeared to predict relative resistance to adjuvant chemotherapy. Humoral and T-cell responses to PEM have been noted in patients with breast cancer and though their prognostic significance remains unclear, preclinical studies have demonstrated that the ability to generate an immune response to peptide or carbohydrate epitopes on PEM can lead to tumour rejection. More recent clinical studies have confirmed that the immune response to such immunogens may be influenced by pretreatment with low dose cyclophosphamide and that ability to develop a specific immune response may influence outcome in patients with metastatic disease.

### SY-4-4 Immunohistochemistry as a Tool for New Prognostic Markers

G. Mac Grogan. *Department of Pathology. Institut Bergonié, 33076 Bordeaux, France*

Technical improvements of the IHC method, including antigen unmasking methods enable utilization of new antibodies and the study of fixed and paraffin-embedded breast cancer fragments. At Institut Bergonie we tested antibodies to ER, PR, P53, c-erbB2, PS2, GSTp and mib1.

- First in a series of 942 invasive ductal carcinomas treated by primary surgery between 1980 and 1986, we found very good correlation, and equivalent prognostic value for the IHC and DCC methods of assessing ER and PR. By multivariate analysis, P53 and c-erbB2 were found to be independent markers of poor prognosis, in the whole group for P53 and the node negative group for c-erbB2. However they were of lesser importance than classical prognostic factors.
- Second in a series of 128 pretherapeutic core biopsies of breast invasive carcinomas treated by primary chemotherapy. Tumor regression was highly correlated to IHC-ER negativity and mib1 strong positivity (> 40%). C-erbB2 was the only independent marker of poor prognosis in this series.
- Last in a series of 208 pretherapeutic core biopsies of breast invasive carcinomas, in post menopausal women treated by tamoxifen. Tumor regression was only linked to PS2 and IHC-ER expression.

Our results show that classical factors are still the most important prognostic factors for breast cancers treated by primary surgery, whereas IHC factors are reliable predictors of tumour response and subsequent outcome, following primary hormono- and chemotherapy.

## SY-5. Adjuvant Treatments for Low Risk Patients (September 12)

### SY-5-1 Risk Determination for Good Prognosis Patients

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Analysis of prognostic factors for low risk breast cancer patients allows identification of those who should be given adjuvant treatment. Classification in this group is based on absence of metastatic nodes in axillary resection. Tumor size is the 1st clinical parameter used to select patients with a very low risk. Analysis of 1018 breast cancers operated at our institute from 1975–1995 revealed that 88% of the tumors < 10 mm size were N-. Disease-free survival for these tumors at 10 and 15 yr was 83% and 79%; overall survival was 87% and 85%. The 2nd parameter influencing management is tumor differentiation (histologic grade, hormone receptor status, DNA ploidy); the 3rd step is assay of proliferative markers (thymidine labelling index, S-phase fraction). Determination of primary tumor cells' potential for invasion and metastasis by search for and assays of certain proteases needed to catalyze or degrade basement membrane directly is now essential. For 246 N– patients at our institute, Cathepsin D did not give us any useful data but the Tumor Angiogenesis Count identified a subgroup with an excellent prognosis regardless of other parameters. Association of urokinase Plasminogen Activator and Plasminogen Activator

Inhibitor in N– breast cancers defines 3 distinct risk populations. Besides differentiating populations with different outcomes, some prognostic factors assist therapy decisions: in NSABP B14 trial, the outcome of good prognosis patients (ER+) was improved by tamoxifen. Over-expression of c-erb B-2 also seems associated with chemotherapy resistance.

### SY-5-2 Selection of Treatment

K.I. Pritchard. *Department of Medical Oncology/Haematology, Toronto-Sunnybrook Regional Cancer Centre and the University of Toronto, Toronto, Canada M4N 3M5*

To date the qualitative values of estrogen (E) and progesterone receptors (PgR) as well as their classification into "positive" or "negative" are the most helpful values available in choosing between chemotherapy and a hormonal approach as adjuvant therapy for low risk patients. Age is also a factor, perhaps because more older women have higher ER and PR values. One possible treatment approach is shown below.

| Patient Group | Risk | | |
|---|---|---|---|
| | Minimal/Low | Moderate | High |
| *Premenopausal* | | | |
| ER positive | no treatment | tamoxifen | chemotherapy* |
| ER negative | – | – | chemotherapy* |
| *Postmenopausal* | | | |
| ER positive | no treatment | tamoxifen | tamoxifen |
| ER negative | – | – | chemotherapy* |

* If chemotherapy refused, tamoxifen may be offered

Of course, for women in whom endocrine and chemotherapy may be equally efficacious, endocrine therapy is almost always to be preferred because it is less toxic. New data from clinical trials however may describe more patient groups in whom both endocrine and chemotherapy may be useful as has been the case for node positive disease.

### SY-5-3 Results of the 1995 Meta Analysis

R. Gray. *UK*

Abstract not available.

### SY-5-4 Trials in Progress and Trials Now Needed

H.J. Senn. *Switzerland*

Abstract not available.

## SY-6. Postmenopausal Breast Cancer (September 12)

### SY-6-1 Treatment of Operable Breast Cancer in the Elderly

I.S. Fentiman. *ICRF Clinical Oncology Unit, Guy's Hospital, London, UK*

In Europe more than one third of patients with breast cancer are aged over 70 and the disease is equally aggressive in older and younger women. Because of increasing life expectancy more cases will be elderly and more will live long enough to develop relapse if treated suboptimally.

Results from clinical trials suggest tamoxifen alone is inadequate primary treatment with a substantial proportion of cases developing progression and relapse. Wide local excision and tamoxifen appear to be as equally effective as a mastectomy in terms of mortality rate. Studies need to be conducted to identify which patients can be treated safely by wide local excision and tamoxifen and others who require more aggressive local treatment such as mastectomy or radiotherapy.

### SY-6-2 Place of Adjuvant Chemotherapy after 50

H. Roché [1]. *Département d'Oncologie Médicale, Centre Claudius Regaud, Toulouse, France*

Adjuvant chemotherapy has been considered as less effective after 50 than before in the first randomized trials. This was explained by Bonadonna as related to a worse compliance to treatment and a lesser dose intensity. The use of anthracyclines did not improved the results (Oncofrance, NSABP–B12). However, the first overview by Peto found out a trend in the reduction of odd ratio death (9% ± 9). In the second metaanalysis, a benefit was observed in the annual death rate (13% ± 4) but with a less extend than for premenopausal patients (24% ± 5).

Similarly, the annual rate of relapse was reduced by 24% (± 3) instead of 36% (± 5) in the premenopausal setting.

It seems evident that this benefit was related also to age. In the 50–59 group, the improvement in the odd ratio relapse was the same (25%) whatever was the menopausal status, but survival was still better for premenopausal patients (13% vs 23%). Between 60 an 69 years old, the benefit was significant for relapses. Unfortunately, the magnitude of trials was too poor to give any judgment after 70.

The combination of chemotherapy and Tamoxifen was superior to chemotherapy alone (–28% relapse; –20% deaths), but better only for relapses when the combination was compared to Tam alone. Conclusions were the same for the negative and positive node groups. Individual trials were not really convincing but the most large ones had the same trend that the meta-analyses (B09, B16, Ludwig III). Major questions are still unsolved: what is the best combination of drugs? Are anthracyclins more toxic after 50?

Is the small absolute benefit of 12% at 10 years justified in view of the not optimal quality of life? Is there a place for chemotherapy after 70?

Finally, the importance of hormonal receptors status has not been clearly determined for the choice in the best treatment for menopausal patients.

### SY-6-3 Skeletal Problems in Postmenopausal Women

M. Tubiana-Hulin. *Centre René Huguenin, 92210 Saint-Cloud, France*

Natural menopause as loss of ovarian function determines acceleration in bone remodeling and subsequent loss of skeletal mass. The outcome is an increase risk of fractures specially in spine, hip and forearm. Highly reproducible measurement of bone mass is now available using single or dual photon or x-ray absorptiometry, quantitative computed tomography or ultrasound. A low bone mass and an accelerated rate of bone loss are predictive of fracture risk and difformities due to microarchitectural abnormalities. Hormone replacement therapy (HRT) is clearly effective in the prevention and treatment of postmenopausal osteoporosis, however, other treatments are also effective and should be used when HRT is contraindicated. In postmenopausal patients, long-term adjuvant Tamoxifen has been shown to protect bone mineral density of low-risk breast cancer patients; a similar effect was observed in patients receiving Tamoxifen in a prevention trial. Non hormonal treatments as calcium, fluoride, calcitonins and various bisphosphonates are investigated in osteoporosis treatment or prevention.

### SY-6-4 Hormone Replacement Therapy

K. Pritchard. *Department of Medical Oncology/Haematology, Toronto-Sunnybrook Regional Cancer Centre and the University of Toronto, Toronto, Canada M4N 3M5*

Replacement therapy (RT) with estrogen (E) or combinations of E and progesterone (P) has traditionally been contraindicated in women with a previous diagnosis of breast cancer. The rationale underlying this recommendation relates to observations from in vitro systems and animal models where, by and large, E is required to maintain breast cancer cell growth. The role of P varies in different in vitro models and animal systems, sometimes acting together with E to promote breast cancer growth and sometimes retarding it. Other pertinent observations include epidemiologic studies of the role of E and E plus P in the etiology of breast cancer. Only a weak relationship between E and the development of breast cancer has been demonstrated, the role of P remains unclear, and it is only with long term use of E (≥ 15 years) that a clear increase in risk of breast cancer development can be consistently demonstrated. With this background and with the diagnosis of a large number of very early breast cancers as a result of screening programs, the dogma that E should not be given with any previous diagnosis of breast cancer is being reexamined. There is limited data examining the role of ERT in women with a previous diagnosis of breast cancer. One can infer however from data about pregnancy following breast cancer and from a few small case series and 2 small case control studies in which E has been given to women with a previous diagnosis of breast cancer that estrogen in this setting may not be as dangerous as has been believed. One randomized study of ERT in this setting is ongoing. Additional data will be required before definitive recommendations regarding ERT in women with a previous diagnosis of breast cancer can be made.