Friday, 22 March 2002 **9:00–9:45**

EUROPA DONNA TEACHING LECTURE

Clinical heterogeneity

314 INVITED

Clinical heterogeneity in breast cancer

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The median survival for patients with metastatic breast cancer is generally 1.5 to 3 years and significantly longer for patients with earlier stages of disease. A vexing problem for medical oncologists treating patients with all stages of disease is the remarkable variation in outcomes seen in otherwise similar patients. If we know a tumor to be aggressive and rapidly fatal we select one type of therapy while if we are confidant in a more indolent course we may chose an alternative plan. Yet our identification of patients is hampered by our lack of understanding of the basis of these differences and a lack of reliability in our predictions. Among patients with the same pathologic stage of breast cancer we can reasonably expect that those with tumors expressing hormone receptors and lacking detectable over-exression/amplification of HER2/neu will likely be less rapidly fatal than those with an opposite pattern. However, even among identified subsets there is still wide variation. Indeed, while the median survival is measured in months the range of survival for newly diagnosed patients can be as short as days or weeks and as long as decades. Understanding the biological basis of this heterogeneity is an important challenge for our community as it is likely to lead to better therapeutics and improved outcomes. This lecture will review the clinical and pre-clnical heterogeneity of breast cancer and discuss several strategies to begin to better understand this phenomenon.

Friday, 22 March 2002 **11:00–13:00**

KEYNOTE SYMPOSIUM

A new look at breast cancer heterogeneity

315 INVITED

Molecular classification of human breast carcinomas using patterns of gene expression

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Human breast tumors show a large amount of diversity in many different properties including their morphologies, clinical histories and in their responsiveness to chemotherapy. This great tumor diversity poses one of the main challenges to the diagnosis and effective treatment of breast tumors. Pathologists and oncologists today currently use a mixture of empirical criteria including cell morphology, measures of the extent of disease dissemination, and a handful of prognostic and predictive markers to assist them in making decisions about treatment regimes. There is a consensus, however, that these methods fall short of the challenges caused by this great tumor diversity. We hypothesized that this phenotypic diversity of human breast tumors would be accompanied by a corresponding diversity in gene expression patterns that we could capture using cDNA microarrays, and that this gene expression diversity might be able to be used to classify tumors into subtypes of clinical and biological importance.

We have now characterized the variation in gene expression patterns in a set of 80 human breast tumors using cDNA microarrays representing at least 8100 genes. Thirty-five of the tumors had been sampled twice, both before and after a 16 week course of doxorubicin monotherapy, and two tumors were paired with a lymph node metastasis from the same patient. The gene expression patterns seen in the repeated tumor samples from the same individual were almost always more similar to each other than either was to any other sample. Sets of co-expressed genes were identified for which variations in mRNA levels could be related to specific features of physiological variation like tumor cell proliferation rates, or to variations in the cellular constituents of the tumors. This group of tumors could be classified into at least five distinct subtypes based solely upon gene expression patterns, and further, we also show that these subtypes were statistically significant predictors of patient outcome and relapse.

316 INVITED

Tailored treatment investigations using predictive factors

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Defining treatment strategies that are more tailored to the specific needs of the individual patient is the ultimate goal of clinical and laboratory therapeutic research. This goal is often thwarted in the adjuvant setting by the need to have a large number of patients in randomised clinical trials and meta-analyses to detect modest treatment effects. The magnitude of treatment effects may differ according to one or more predictive factors so that results for the average patient may not be appropriate for treatment decisions regarding the individual patient. Tamoxifen is not beneficial for premenopausal women, unless they have an endocrine responsive tumour. Patients with hormone receptor-positive tumours do better than patients with hormone receptor-negative tumours, unless they are very young (e.g., 34 years or less) and receive chemotherapy alone without endocrine therapy. Patients with HER2-neu positive advanced disease do worse than those without HER2-neu overexpression, unless they receive trastuzumab. Postmenopausal women derive little benefit from chemotherapy, unless their tumour does not express ER. Historically, randomised trials and treatment guidelines have defined patient cohorts according to prognostic factors that characterize the background level of risk of relapse against which the benefits and burdens of adjuvant therapies are weighed. More recent guidelines focus on subpopulations characterized by factors that predict response or non-response to a specific treatment modality. Endocrine therapies and endocrine effects of chemotherapy should be studied in patients with endocrine responsive disease, while chemotherapy questions should be the focus for endocrine non-responsive cohorts. Examples of data analyses and study designs for tailored treatment investigations will be presented. In the adjuvant setting, subpopulations of particular interest include premenopausal women with endocrine responsive disease, postmenopausal women with endocrine responsive disease, all women with endocrine non-responsive disease and all women with tumours overexpressing HER2-neu.

317 INVITED

Is progress changing the priorities and needs of individual patients?

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It is estimated that each year one million women worldwide develop breast cancer; in the European Union alone, some 250,000 women are diagnosed and more than 60,000 women die of the disease. Factors influencing outcomes include variations in national and regional resources, healthcare systems and socio-economic priorities. Poorer survival of breast cancer patients from disadvantaged social classes reflect lower standards of education and nutrition, impoverished lifestyles, little or no access to quality care and poor patient-doctor communication.

Recent years have seen significant advances in understanding and management of breast cancer and the introduction of specific recommendations for the development of optimal practice within specialist breast units. At the same time, there has been an explosion of public information on breast cancer of varying degrees of accuracy and value to the patient. Many patients and healthcare professionals consider that this is bringing about as much confusion as education, as well as changing the doctor-patient relationship and perceptions of traditional clinical practice.

Patients' priorities and needs as determined in the Caring about Women and Cancer survey (CAWAC) (Veronesi, von Kleist et al 1999) and its precursor Parcours de Femmes (Serin et al 1994) will be discussed in the context of new horizons in breast cancer detection, diagnosis and management.