Section introduction

Introduction: challenging established dogma

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Mr Michael Dixon [1] examined whether neoadjuvant endocrine or chemotherapy might interfere with the assessment of prognostic factors that are normally used to predict prognosis in patients with breast cancer. The major components for prognosis include tumour size, node status, tumour grade, oestrogen receptor (ER) status, and HER2/neu status. Newer prognostic factors include changes in tumour parameters before and after neoadjuvant therapy. The major parameters are Ki67 index, change in gene expression during treatment and changing tumour size during treatment.

Mr Dixon concluded that one would be able to measure tumour size accurately at the time of diagnosis with magnetic resonance imaging, ultrasound, or clinical measurement. In the discussion period the question was raised whether these three parameters can, in fact, accurately predict overall tumour size. With accurate ultrasound and fine needle aspiration (FNA), it might be possible to detect nodal status at the time of neoadjuvant therapy. However, sentinel node techniques have not been used in this setting, and some concern about the use of ultrasound and FNA was raised during the discussion. A key aspect of the presentation was that other parameters might provide additional predictive factors. For example, reduction in tumour size, Ki67, or other parameters during neoadjuvant therapy might provide additional information about ultimate prognosis.

Dr Craig Allred [2] reviewed the evidence for and against the possibility that all breast cancers arise from ER-positive precursors. This has been a subject of major controversy regarding the stem cells or transitional cells that give rise to breast cancer. After his review, Dr Allred concluded that some ER-negative breast cancers probably arise from ER-positive precursors, and that some ER-positive tumours arise from ER-negative cells. He indicated that a key practical issue is the need to develop means to convert ER-negative to ER-positive tumours to enhance responsiveness to hormonal therapy. During his presentation, Dr Allred provided striking histological evidence that a great deal of heterogeneity exists within individual tumours. Within one tumour, there may be coexisting portions that are grade I, II, or III and areas that are ER-positive and other areas that are ER-negative. He indicated that this phenomenon must be taken into account when interpreting cDNA array data or other molecular techniques that utilize the entire tumour for analysis.

Dr Carol Fabian [3] discussed use of surrogate end-point biomarkers to assess prognosis and the risk for developing breast cancer in patients. She focused her remarks on the ability of random, peri-areolar fine needle aspirations to detect intraepithelial neoplasia or atypical ductal hyperplasia. In her experience, these techniques are associated with minimal discomfort and feasible in large numbers of women. She reviewed her experience with arzoxifene, a third-generation selective ER modulator, in comparison with placebo. There was no change in cytomorphology index score, but there was a significant favourable modulation of mammographic breast density, breast tissue ER expression and serum insulin-like growth factor (IGF)-1/IGF binding protein-3 ratio. These changes were more marked in premenopausal than in postmenopausal women. Dr Fabian then commented that the major source of oestrogen in postmenopausal women is direct *in situ* production in the breast. Accordingly, it might be possible to give an aromatase inhibitor plus hormone replacement therapy (HRT). A study is currently examining this possibility.

Professor William Miller [4] then evaluated whether changes in genes regulated by oestrogen in breast cancer cells might provide predictive information regarding responsiveness to aromatase inhibitors. He reviewed the gene array results in five separate studies with cell lines and with his own data in patients receiving neoadjuvant therapy. It would appear that there are major differences among studies with respect to the genes identified to be oestrogen responsive at the present time. These genes do not predict breast cancer responsiveness. He noted that the nine most commonly quoted oestrogen-regulated genes in MCF7 cells were *NRIP1*, *STC2*, *CCND1*, *MYB* and *TFF1* (which are downregulated), and *ARK4*, *IGFBP4*, *SCL7A5* and *TPD52-1* (which are

relatively unaffected by treatments in both responders and nonresponders). He concluded that oestrogen-regulated genes are molecular markers of oestrogen sensitivity (but not dependence). He further concluded that expression profiles and molecular responses to endocrine therapy in clinically resistant tumours may be similar to those in clinical responders, and therefore that most oestrogen-regulated genes are unlikely to be robust markers of clinical response and therapy.

Dr Richard Santen [5] then reviewed an hypothesis that he called the 'oestrogen paradox'. This concept suggests that short-term oestrogen (without concomitant progestin) reduces the risk for breast cancer and long-term use increases the risk. He reviewed the epidemiological data from the Women's Health Initiative study, the Nurses Health Study, the Lyytenen study and others that indicate that short-term oestrogen is associated with a trend toward a decrease in breast cancer risk. Long-term use of oestrogen in the Nurses Health Study and others was associated with an increased risk for breast cancer.

The hypothesis to explain this oestrogen paradox is that oestrogen causes apoptosis in cells adapting to long-term oestrogen-deprivation therapy. On the other hand, long-term exposure to oestrogen causes an increased number of mutations both through ER-mediated increases in cell proliferation and through direct genotoxic effects of oestrogen. Underlying this thinking is that there is a reservoir of undiagnosed tumours (approximately 6%) in women starting HRT, and that these tumours can respond to oestrogen in the short term with apoptosis and a reduced detection rate over the next 5 to 9 years. Dr Santen noted that direct demonstration of oestrogen-induced apoptosis in occult breast cancers in women will be critical.

Finally, Dr Craig Jordan [6] reviewed data regarding oestrogens in patients with breast cancer. He initially presented information regarding tamoxifen and use of oestrogens as breast cancer therapy. The major emphasis was on the fact that substantial data exist to show that high-dose oestrogens cause tumour regression in patients with heavily treated hormone-dependent breast cancer. His group has conducted a number of studies *in vitro* and *in vivo* to show that oestrogens induce apoptosis. He indicated that during the process of development of drug resistance, the component of oestrogen-induced apoptosis becomes evident. Recognition of the new biology of oestrogen action that causes apoptosis in tumours developing hormone resistance now opens up an unanticipated door of opportunity to exploit the findings in patients. He proposes that periodic 'oestradiol purge' will deplete tumours of cells that are resistant to tamoxifen or aromatase inhibitors. His group has now received a large Department of Defense Centers of Excellence grant to study this hypothesis in patients with breast cancer.

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