385 POSTER

Arimidex, tamoxifen alone or in combination (ATAC) adjuvant trial in post-menopausal breast cancer

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Purpose: The ATAC trial is a double blind study, designed to compare the efficacy and safety of tamoxifen alone, Arimidex (anastrozole) alone, and the combination of tamoxifen plus anastrozole, as adjuvant treatment in post-menopausal women with early breast cancer, who have completed primary therapy. Treatment will be for 5 years or until first recurrence. The dose of tamoxifen is 20 mgs od and anastrozole 1 mg od.

Methods: Patients must be post-menopausal, have histologically proven operable breast cancer, have completed all primary treatment (surgery ± radiotherapy ± chemotherapy), and also be candidates for adjuvant hormonal therapy. The trial aims to enrol 7500 patients and more than 3700 had been recruited by the end of March 1998. The endpoints are time to recurrence of breast cancer, overall survival, and safety and tolerability.

Five sub-protocols will provide additional information on quality of life, bone changes, endometrial changes, lipid profiling and pharmacokinetic evaluation in each treatment arm.

Results: Demographic information available on the first 1255 patients recruited, showed 52% were 50–65 years of age and 42% over 65 years of age; 44% of tumours were stage I; 64% were ER+, 42% were PR+ and 5% ER−PR−.

Conclusion: Thus far demographic characteristics are in agreement with the patient population detailed in the protocol. The status of the main trial and subprotocols will be updated.

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386 POSTER

Endometrial changes caused by tamoxifen

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Purpose: Prolonged therapy with tamoxifen gives rise to endometrial abnormalities and has been reported to increase the subsequent development of endometrial cancer six fold. This prospective study was designed to examine the time course over which endometrial abnormalities occur in an adjuvant setting.

Methods: Patients requiring adjuvant tamoxifen as part of their normal treatment for breast cancer underwent baseline pelvic examination, transvaginal ultrasound scanning (TVUS) to measure endometrial thickness (ET) and biopsy for histology and insulin growth factor-1 levels if ET was > 7 mm. Subsequent TVUS (and biopsy if ET > 7 mm) was performed at 1, 2, 3, 6, 12 and 24 months.

Results: Twenty four patients have been studied for a mean of 10 months. The mean endometrial thickness has increased from 3.2 mm before tamoxifen (0 months) to 5.1, 7.1, 5.2, 4.9, 6.2 and 6.9 mm at 1, 2, 3, 6, 12 and 24 months. After 6 months therapy with tamoxifen, 27.3% of women had an increase in endometrial thickness of >100% and this had risen to 54% of women after 12 months therapy.

Conclusion: Tamoxifen causes a rapid initial rise in endometrial thickness, perhaps due to oedema, but then continues to increase endometrial thickness progressively and in a larger proportion of patients with increased duration of use.

387 POSTER

Adrenomedullin: A potential autocrine growth factor for human breast epithelial cells during development and carcinogenesis

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Adrenomedullin (AM) is a potent hypotensive peptide that was originally isolated from a human pheochromocytoma. AM has a variety of biological effects that include vasodilation, natriuresis, bronchodilation, anti-secretagogue, neurotransmission, and growth regulation in a variety of cells. Published data using MCF-7, a breast cancer cell line, showed both AM mRNA and protein expression, and in vitro studies showed specific growth regulation by AM, using an AM MoAb-G6 (Miller, MJ et. al., JBC 271: 23345–23351). In addition, we have also published data that demonstrates AM's role in mammary development. We show that AM mRNA and protein is present in all stages of breast development, and the milk contained within the lactating duct showed an AM-like entity by Western blot analysis (Jahnke, GD et al., J Mol Endocrinology 19: 279–289). In this study we investigate the functional role of AM in human breast tissue and in several breast cancer cell lines. We have identified AM mRNA expression in 4/4 normal and 6/6 malignant breast cell lines using RT-PCR. Immunohistichemical and in situ RT-PCR analysis of paraffin embedded tissue localized AM expression to epithelial cells in 11/11 normal specimens. On the basis of our previous in vitro studies with MCF-7 and growth inhibition with AM MoAB-G6, we investigated a similar course with an in vivo model. MCF-7 xenografts in nude mice were significantly reduced in volume by 30% after injection of AM Moab-G6. We have demonstrated that human breast milk contains an AM-like (6 kDa) entity by Western blot analysis that will be sequenced to verify it is authentic AM.

388 POSTER

A pure antiestrogen, ICI 182,780, stimulates the growth of tamoxifen-resistant KPL-1 human breast cancer cells in female nude mice

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Antiestrogen-resistance frequently occurs during the treatment of breast cancer. The critical mechanism responsible for this resistance has not yet been elucidated. We established a human breast cancer cell line, KPL-1, derived from a patient with a recurrent disease which had appeared under tamoxifen administration. Our previous study suggested that this cell line is estrogen receptor (ER)-positive but tamoxifen-resistant (Br J Cancer 71: 845–853, 1995). The effects of a pure antiestrogen, ICI 182,780, were investigated in this study. Although tamoxifen inhibited neither cell growth nor estradiol-stimulated transcriptional activity, ICI 182,780 significantly inhibited both of these. Tamoxifen and ICI 182,780 were administered to female nude mice bearing KPL-1 tumors. Tamoxifen had no effect on tumor growth, but ICI 182,780 unexpectedly stimulated tumor growth ($P = 0.022$). In addition, estradiol administration tended to inhibit tumor growth ($p = 0.198$). To the best of our knowledge, this KPL-1 cell line is the first breast cancer cell line to be growth-stimulated by ICI 182,780 and growth-inhibited by estradiol in vivo. To explore the possible causes of these novel phenotypes, the mRNA levels of ER-α, ER-β, some growth factors, and their receptors in KPL-1 cells were compared with those in three other ER-positive human breast cancer cell lines (MCF-7, T-47D, and KPL-3C) by a semiquantitative RT-PCR. Fibroblast growth factor (FGF)-1 was overexpressed only in the KPL-1 cell line. Taken together with the results of our previous study suggesting that overexpression of FGF-1 or -4 induces breast cancer progression (Breast Cancer Res Treat 31: 153–165, 1994), paracrine interaction between tumor cells and stromal cells mediated by growth factors, such as FGF-1, might be a key factor to explain the unique hormone-responsiveness of KPL-1 cells.

389 POSTER

Androstenedione (A) conversion in lymphocytes infiltrating breast cancer (BC) tissue

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Estrogens are involved in breast carcinogenesis. Previously we described 3-component model of estrogenic pool formation in BC tissue which suggested the participation of lymphocytic-macrophagal infiltrate in the process (Berstein, Santen, Santner: Med. Hypotheses, 1995). In this work we isolated lymphocytes from tumor tissue, TIL (enzymatic digestion), evaluated in them conversion of A (^3H_2O-release assay) and compared data with aromatase (Arom) activity in the whole tissue. Material for study included 32 samples of BC tissue. In the part of samples isolated lymphocytes (because of their small number) were combined. Totally 18 TIL samples were analyzed (5 from pts with preserved menstrual cycle/I/ and 13 from pts in menopause/II/). Number of lymphocytes isolated from tumors and percent of tumor cells in lymphocytic suspension were higher in I than in II. On the contrary, A conversion in tumor lymphocytes (fM/mg prot or fM/l mln cells) was higher in group II. Positive correlation between A conversion