had no further effect in increasing the sensitivity to oxidative stress. Taken together, these results suggest an important role for Prx II and Prx III in the protection of cells against oxidative stress in general and in the mechanism of lung metastasis in particular.

Future studies will explore the importance of the different cellular redox pathways in the metastatic process by further silencing (thioredoxin) or chemically blocking (catalase, glutathione system) various members of the redox system.

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421 Poster

An electronic data registry for the evaluation of fulvestrant in clinical practice

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Fulvestrant ('Faslodex') is currently licensed for the treatment of post-menopausal women with advanced breast cancer following relapse or progression on antioestrogen therapy. However, it is unclear how this agent is being used in clinical practice. An electronic data registry was developed to provide insight into current fulvestrant usage and to collect clinical outcomes data. The electronic registry was designed by MedNet Solutions, which enabled participating centres to enter data via a secure Internet site. Data from 213 patients from 34 physician practice sites were submitted, of these 196 patients (92%) have now discontinued fulvestrant treatment and 17 patients (8%) are ongoing. Almost all patients (200; 94%) had received prior endocrine therapy including tamoxifen, anastrozole, exemestane, letrozole, toremifene, or megestrol acetate. One-hundred-and-thirteen patients (53%) had prior exposure to tamoxifen, of these 51 (45%) had metastatic disease that had progressed on tamoxifen. A total of 1500 fulvestrant injections have been administered with patients receiving a mean of seven injections (range: 1–31). One-hundred-and-two patients (48%) gained clinical benefit (CB, complete response [CR, n = 3], partial response [PR, n = 52] or stable disease ⩾24 weeks [n = 47]) with fulvestrant treatment. In patients experiencing a CR or PR the median time to response was 2.0 months (range: 0.6–8.3 months) and the median duration of response was 4.7 months (range: 0.9–21.9 months). One hundred and fifty-eight patients (74%) have now progressed with a median time to progression of 4.6 months. Of the 196 patients who have completed fulvestrant treatment, 155 (79%) have received subsequent therapy, most commonly chemotherapy (55%). The electronic registry is a useful tool to monitor usage of fulvestrant and obtain outcomes data in clinical practice. These data support previous observations that fulvestrant lacks cross-resistance with other commonly used endocrine treatments and is a valuable new addition to the endocrine treatment sequence for patients with advanced breast cancer.

422 Poster

Characterization of brain metastasis from human breast cancer in nude mice: longitudinal MR studies at 7 Tesla

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The current incidence of brain metastases seems to be the paradoxical result of the effectiveness of drugs that do not cross the blood-brain barrier (BBB). The aim of this study was characterize in vivo functional phenotypes that might be correlated with enhanced resistance to therapy in brain metastasis. For this, we optimized a model of brain metastasis by internal carotid injection of brain metastatic cells (435-Br1) from a well known breast cancer cell line MDA-MB-435, from which we had previously identified 19 differentially expressed proteins. We obtained morphologic and metabolic magnetic resonance (MR) analyses at high-field (Bruker PharmaScan, 7.0 Tesla). Tumour growth in female BALB/c nude mice was characterized by T2, CE-T1 (Gd-DTPA, i.v. 0.2 mmol/kg) and diffusion weighted imaging (b = 100, 400, 800 s/mm^2), and also by single voxel 1H MRS (TE 35 and 136 ms). Metastases were detected in vivo at different progression stages by T2 and CE-MRI in 5 of 7 mice inoculated. ADC maps showed higher values for metastasis than for non-afflicted tissue: 0.89±0.07 and 0.55±0.02 ($\times 10^{-3}$ mm^2/s), respectively, implying low tumour cellularity as confirmed by histology. MRS pattern changes indicate replacement of normal brain parenchyma by aggressive tumour cells (high Cho, low NAA). Tentative pattern recognition analysis of selected spectra, carried out in a Decision Support System (DSS) developed for human brain tumour spectra classification, INTERPRET SV (http://azizu.uab.es/INTERPRET), placed the spectral patterns in a clear progression towards malignancy, resembling human cases of healthy tissue being replaced by low grade glial and finally evolving towards an aggressive pattern (GBM/metastasis). IHC analyses of tissues led us to the assessment of the specific protein expression in metastasis induced by brain microenvironment. In conclusion, we have characterized by MRI and 1H MRS a model of brain metastasis developing a possible non-invasive tool for brain metastasis staging and grading in animal models to use in experimental treatments.

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423 Poster

Fulvestrant in postmenopausal women with metastatic breast cancer progressing on prior endocrine therapy – updated results from an expanded access programme

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Background: Fulvestrant ('Faslodex') is an oestrogen receptor (ER) antagonist with no agonist effects. Fulvestrant downregulates the ER, which leads to reduced cellular levels of progesterone receptor (PgR). This abstract reports the results of an expanded access programme in the Czech Republic (supported by AstraZeneca) in which postmenopausal women with metastatic breast cancer whose disease had progressed on prior endocrine therapy were treated with fulvestrant 250 mg.

Methods: Fulvestrant 250 mg was given as a single 5 mL intramuscular injection, once every 28 days until disease progression or other event necessitating withdrawal. Tumour response was assessed monthly using Union Internationale Contre le Cancer criteria. Time to progression (TTP) was defined from start of treatment until objective disease progression. Duration of response (DOR) was defined, for responding patients only, as the time from treatment initiation to disease progression.

Results: Between 8/2001 and 4/2005 a total of 64 patients (median age 66 years [range 39–92 years]) were treated in our centre. 87% of patients had ER-positive and/or PgR-positive disease. All had received prior endocrine treatment for advanced disease and 62% had received adjuvant endocrine treatment. Forty-one patients (64%) had also received prior chemotherapy. Thirty-two patients (50%) were receiving fulvestrant as their 3rd- or 4th-line endocrine treatment for advanced disease. Five patients (8%) had an objective response (1 CR and 4 PR(. All responses were greater than 90 weeks in duration. Thirty four patients (53%) had stable disease (SD) ⩾24 weeks giving an overall clinical benefit rate (CR +PR + SD ⩾ 24 weeks) of 61%. The median TTP was 26 weeks. Fulvestrant 250 mg was well tolerated and no WHO grade III/IV toxicities were observed.

Conclusion: Fulvestrant 250 mg is an endocrine agent with demonstrable efficacy and a very favourable tolerability profile in patients with advanced breast cancer. The monthly injection schedule supports both close patient monitoring and good compliance. Fulvestrant offers clinicians a new option for the treatment of postmenopausal women with advanced breast cancer progressing on prior endocrine therapy.

424 Poster

Every two-weeks docetaxel in the treatment of elderly patients with advanced breast cancer

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Background: The study was conducted to investigate the efficacy and toxicity of bi-weekly docetaxel administration in elderly metastatic breast cancer patients.

Patients and Methods: Women aged ⩾65 years with histologically confirmed metastatic breast cancer were eligible for enrollement. Patients could have received prior systemic adijuvant chemotherapy. Docetaxel was given as first-line (after adjuvant chemoteraphy) in 10 patients and as second-line in 21 patients; 10 patients were pre-treated with antracyclines regimens. Docetaxel was administered at 50 mg/m^2 as 1-hour intravenous infusion every 2 weeks. Docetaxel dose was reduced by 25% for grade 2 neurologic toxicity, febrile neutropenia, grade 3 thrombocytopenia or of any grade 2 non-haematologic toxicity. Patients were premedicated with dexamethasone 4 mg i.m. taken the night before, mornig of, and evening after treatment. Patients continued to receive treatment until they developed either undue toxicity or until the time of disease progression.

Results: A total of 31 metastatic cancer women were entered into this study. The median age was 72 (range 65–78). ECOG performance status for all patients was 0–1. Most patients (21) had received prior chemotherapy, 10 patients had received first line anthracycline containing regimens. A total of 374 infusions were administered, 13.3 median, with a cumulative dose of 18,420 mg/m^2 (1083 mg/m^2 median). The projected

dose intensity was 25 mg/m^2/week and the median dose intensity (MDI) received was 23.2 mg/m^2/week with a median relative dose (MRD) of 0.93. Two patients (6.4%) showed CR,10 patients (32%) showed PR, which accounted for 38.7% of the objective response rate; 5 patients (16.1%) showed SD > 6 months; taking this patients into account, 54% showed clinical benefits; of the responders five have been treated with anthracycline and six have received only adjuvant chemotherapy; 14 patients (45.1) showed PD. The median time to progression was 36.2 weeks and the median survival time was 18 months.

Treatment was generally well tolerated. Five patients (16%) required delay of treatment for neutropenia. Four patients (12.9%) showed grade 2 of stomatitis; five patients (16%) showed grade 1 of fluid retention; 8 patients(25.8%) showed grade 1–2 of fatigue and 3 patients (9.6%) showed grade 1 alopecia. 3 patients (9.6%) with concomitant fluid retention and fatigue requiring dose reduction at 7th, 8th and 10th infusion (tab 2). Nail changes where uncommon (1 patient) and mild.

Conclusion: The data reported confirmed the efficacy of docetaxel in the treatment of advanced breast cancer; the more favourable toxicity profile than 3-weekly (myelodepression) and weekly (fatigue) schedule registered suggest that the two weeks schedule could be routinely administered in the elderly patients or in those patients with low performance status.

Thursday, 23 March 2006 16:00–16:45

POSTER SESSION

Targeted treatment

425 Poster

SU11248 (sunitinib malate) therapy in patients with refractory metastatic breast cancer: preliminary safety and efficacy results from a phase II study

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Introduction: SU11248 is an oral, multi-targeted tyrosine kinase inhibitor of multiple receptors important in signaling pathways fundamental to tumor growth and survival including PDGFR, VEGFR, KIT, and FLT3. Progression of breast cancer (BC) is dependent on angiogenesis, a process stimulated by autocrine and paracrine signaling involving VEGFR and PDGFR. Results are reported here from a phase II study of SU11248 monotherapy in patients (pts) with previously treated metastatic BC.

Methods: Female pts with unresectable histologically/cytologically confirmed breast adenocarcinoma received oral SU11248 (50 mg/day) for 28 days followed by 14 days off treatment to comprise a 6-week cyclical regimen. Toxicity-related dose reduction was permitted. Response rate was assessed every 2 cycles by RECIST and was the primary endpoint. A total sample size of 63 was required to identify a clinically meaningful ORR ⩾15% based on Simon's Minimax 2-stage design.

Results: A total of 64 pts (median age 51 years) were enrolled. The majority of pts, 83%, had visceral disease; 61% and 17% were ER+ and HER2+, respectively. Fifty-two pts had received prior adjuvant chemotherapy (anthracycline 90%, taxane 56%) and in the MBC setting 61 pts were previously treated with anthracycline (26%), taxane (69%), capecitabine (66%), vinorelbine (23%), platinum (16%), and gemcitabine (15%). Overall, patients received a median of three prior chemotherapy regimens. The most frequently reported non-hematological grade 2/3 adverse events (AEs) were fatigue (41% and 14%, respectively), diarrhea (20% and 6%, respectively), and nausea (16% and 8%, respectively). Most frequent grade 2/3 hematological AEs were neutropenia (27% and 34%, respectively; no cases of neutropenic fever), anemia (17% and 16%, respectively) and thrombocytopenia (16% and 3%, respectively). One grade 4 AE was reported (neutropenia, which did not result in neutropenic fever). Of the 58 pts who experienced AEs, 24 (38%) required toxicity-related dose-reduction and 34 (53%) required dose interruption. In all, seven pts (11%) achieved a partial response of between 11 and 32 weeks duration. A further three pts (5%) achieved stable disease for ⩾6 months.

Conclusions: SU11248 has significant single-agent activity and acceptable toxicity in pts with refractory MBC. Toxicity is manageable with dose reductions and/or interruptions. Future studies should include less heavily pre-treated pts and alternative dosing and combination regimens.

426 Poster

Curcumin potentiates effect mediated by paclitaxel in breast cancer: in vitro & in vivo study

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Cancer chemotherapeutic strategies should be devised to provide higher tumor response and lower toxicity. Paclitaxel is the best anticancer agents isolated from plants, but its major disadvantage is its dose-limiting toxicity. The molecular basis of resistance to paclitaxel is not well understood, although mounting evidence supports the role of constitutive activation of NF-κB and thereby affording protection against cell death. Curcumin has been shown to inhibit the growth of various cancer cells in vitro and in vivo without toxicity to normal cells. The antitumor effects of curcumin could be in part due to inactivation of NF-κB activity. We hypothesize that blocking NF-κB activity may augment paclitaxel cancer chemotherapy. In this study, we investigated whether the inactivation of NF-κB by curcumin would enhance the efficacy of paclitaxel for breast cancer in vitro and in vivo.

MDA 231 GFP breast cancer cells were treated with curcumin, paclitaxel, and paclitaxel and curcumin combination. MTT assay, apoptosis assay and IκBα western blot assay (NF-κB activity) were performed. Curcumin dose-dependently decreased tumor proliferation and increased tumor apoptosis. MDA 231 GFP breast cancer cells were treated with 10 nM paclitaxel, 1 μM curcumin, 10 nM paclitaxel and 1 μM curcumin combination. Paclitaxel induced activation of NF-κB, but curcumin did not, and curcumin restored the NF-κB activation induced by paclitaxel. The combination of 1 μM curcumin with 10 nM paclitaxel elicited significantly greater inhibition of cell growth compared with either agent alone. The combination treatment induced more apoptosis in MDA 231 GFP cells compared with single agents. Moreover, in experimental breast cancer murine model using MDA 231 GFP cells combination therapy with paclitaxel and curcumin significantly reduced tumor size and decreased tumor cell proliferation, increased apoptosis and decreased expression of MMP-9 (down stream of NF-κB signaling pathway) compared with either agent alone.

These results clearly suggest that curcumin combination, which inactivates NF-κB activity, may contribute to increased cell growth inhibition and apoptosis augmenting paclitaxel chemotherapy, which could be a novel strategy for the treatment of breast cancer.

427 Poster

Modulation of target therapy by estradiol in tamoxifen-resistant breast cancer cells

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Tamoxifen has been used as a main hormonal agent not only for the treatment of breast cancer but also for the prevention of the disease. Tamoxifen resistance is the major obstacle in hormonal therapy for breast cancer and the development of resistance was reported to be associated with HER2 or EGFR. To overcome tamoxifen resistance, clinical trial with trastuzumab or ZD1839 is ongoing. We had established a tamoxifen-resistant cell line with T47D:A18 breast cancer cells by long-term treatment of tamoxifen (1 μM). The resistant cell, T47D:A18/4-OHT, showed significant changes from estrogen dependent to partially dependent in cell growth pattern and from negative to positive expression of HER2. In this study, trastuzumab, humanized monoclonal antibody to extracellular domain of HER2 receptor, and ZD1839, EGFR tyrosine kinase inhibitor, were applied to the resistant cell, and Cell growth assay was performed to investigate their effects on growth of tamoxifen resistant cells. The changes of HER2 expression was confirmed by Western blotting. In the results of growth assay, each of them showed inhibitory action on growth of T47D:A18/4-OHT cells, but no synergistic action by the combined treatment with tamoxifen. Treatment of estradiol (1 nM) alone showed promoting action on growth of T47D:A18/4-OHT cells, however, unexpectedly co-treatment of estradiol (1 nM) with trastuzumab or ZD1839 revealed additional inhibitions of T47D:A18/4-OHT cell growth. Taken together, estradiol showed different roles in regulation of tamoxifen-resistant T47D:A18/4-OHT breast cancer cells according to changes in growth factor receptor signaling. This fact might be a clue to overcome tamoxifen resistance in the treatment of breast cancer.