heterodimers and downstream signalling through ERK1/2 MAPK to phosphorylate cPLA2α on Ser505. Over-expression or amplification of HER2 is found in approximately 30% of breast cancer patients and correlates with a poor clinical outcome and resistance to endocrine therapy. We have found an increased expression of cPLA2α at both mRNA and protein levels in SKBR3 breast cancer cells over-expressing EGFR and HER2, as compared with MCF-7 cells which have low expression of EGFR and HER2. The increased protein expression of cPLA2α in SKBR3 was accompanied with a two-fold increase in enzymatic cPLA2α activity. Inhibition of HER2 with either the monoclonal antibody Trastuzumab or short-interfering RNA caused a reduction in both total and phosphorylated levels of cPLA2α in SKBR3. Pharmacological blockade of cPLA2α with the specific inhibitor (525143) impacted on cell growth of SKBR3 cells, by reducing E2-induced proliferation and inducing both apoptotis and necrosis. Selective gene silencing of cPLA2α also reduced both E2-dependent and E2-independent cell growth. To investigate the clinical significance of our in vitro studies, we analysed cPLA2α expression by real time qRT-PCR in tumor samples from HER2-negative and HER2-positive breast cancer patients: our preliminary data show a significant increase in cPLA2α in tumor samples over-expressing HER2. This study highliths cPLA2α as a potential target for therapeutic intervention in HER2-positive breast cancer.

35LBA LATE BREAKING ABSTRACT

Zoledronic acid affects the ability of mesenchymal stem cells to sustain breast cancer progression

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Background: Zoledronic acid (ZA) very rapidly concentrates in the bone following intravenous administration. ZA has been recently shown to increase the progression free-survival of estrogen receptor (ER)-positive breast cancer patients by reducing both loco-regional and distant metastases. Recent reports have also shown that bone-marrow-derived mesenchymal stem cell (MSCs) are recruited to the stroma of developing tumors, where they increase the metastatic potential of breast cancer cells by secreting the chemokine RANTES (CCL5) that sustains breast cancer motility and invasion.
Materials and Methods: The antiproliferative effects of ZA on human primary MSCs were evaluated with an anchorage-dependent growth assay. The effects of ZA on the secretion of RANTES, IL-6 and angiogenic factors were assessed by using the Luminex-based Bio-Plex Suspension Array. The ability of MSCs and breast cancer cells to migrate through a fibronectin-coated membrane was evaluated by using a commercially available assay.
Results: We found that treatment with ZA produced marginal effects on the growth of human primary MSCs, with an approximately 25% growth inhibition following treatment with 20 μM ZA for 48 hours. In contrast, treatment with similar concentrations of ZA almost completely suppressed the ability of MSCs to secrete RANTES. The effect of ZA on RANTES was quite specific, since marginal inhibition of the secretion of different angiogenic growth factors, such as VEGF, IL-8 and bFGF, was observed. ZA also significantly reduced the secretion by MSCs of IL-6 that has been previously demonstrated to act as a potent paracrine growth factor for human breast cancer cells. Conditioned medium from ZA-treated MSCs showed a reduced ability to promote the migration of ER-positive MCF-7 breast cancer cells through a fibronectin-coated membrane as compared with conditioned medium from untreated cells. In co-culture assays, treatment with ZA reduced the ability of MSCs to sustain the growth of breast cancer cells. Finally, the migration of MSCs was significantly reduced by ZA.
Conclusions: Taken together, these data suggest that ZA might exert its antitumor activity in the bone marrow microenvironment by inhibiting the migration of MSCs and by blocking the ability of MSCs to secrete factors involved in breast cancer progression.

36LBA LATE BREAKING ABSTRACT

Long-term safety and tolerability of fentanyl pectin nasal spray in opioid-tolerant patients in the treatment of breakthrough cancer pain

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Background: The authors are submitting this abstract on behalf of the Fentanyl Nasal Spray Study 045 Investigators Group. Placebo-controlled, randomized controlled trials have demonstrated efficacy with a rapid onset of effect for fentanyl pectin nasal spray (FPNS), a new nasal formulation of fentanyl. The aim of this study was to assess the long-term safety and tolerability of FPNS in treating patients with breakthrough cancer pain (BTCP).
Material and Methods: Patients (new and rolled over from previous controlled studies) with cancer experiencing 1−4 episodes/day of BTCP whilst taking ⩾60 mg/day of oral morphine (or equivalent) for cancer pain were eligible to enter an open-label safety study: 16-week initial phase and extension phase. FPNS was used to treat up to 4 BTCP episodes/day. Safety and tolerability were assessed by: adverse events (AEs), withdrawal due to AEs and nasal assessments. Objective nasal assessments examined treatment effect on the nasal mucosa. Subjective nasal assessment included: stuffy/blocked nose, runny nose, itching/sneezing, crusting/dryness of nose, burning/discomfort, nasal bleeding, cough, postnasal drip, sore throat and taste disturbance. Additional rescue medication use was also recorded.
Results: 403 patients (234 new, 47 exposed to FPNS during titration phase but did not enter the treatment phase, 122 rolled over) were included in the safety analysis (42,227 FPNS-treated episodes) with 110 patients completing the full 16 weeks. For the entire course of the study, mean duration of treatment was 60 days, with 138 patients treated for ⩾90 days. A total of 99 (24.6%) patients reported treatment-related, treatment-emergent AEs (TEAEs) that were generally mild or moderate in severity. TEAEs were not dose related and were typical of opioid therapy. Of the 80 deaths that occurred during the study, 1 death was possibly related to study drug (constipation, intestinal perforation, peritonitis). Nonfatal serious AEs were reported in 61 (15.1%) patients – 6 possibly and 1 probably related to study drug. Of the 20 patients who discontinued treatment due to an AE, 9 patients withdrew due to treatment-related AEs. Objective and subjective nasal assessments revealed no clinically significant effects. 94% of FPNS-treated episodes required no rescue medication and 90% of patients required no dose change.
Conclusions: FPNS was safe and well tolerated both systemically and nasally. Overall, FPNS delivered consistent and reliable clinical effects that were sustained through up to 4 months of BTCP treatment.

37LBA LATE BREAKING ABSTRACT

Impact of p53 protein overexpression on survival of stage II young breast cancer patients

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Background: p53 is a tumor suppressor gene and plays important role in the etiology of breast cancer and has been linked to breast cancer survival. The prognostic potential and impact on 5-year survival of p53 protein overexpression was investigated in 34 primary breast cancers from stage II young breast cancer patients (<50 years).
Material and Methods: using archived tumor tissue from 34 patients diagnosed with stage II breast cancer between 2001–2003, we determined p53 protein overexpression by immunohistochemistry. We examined the association of p53 overexpression and HER2 scores, ER/PR status and anthracyclines doses in adjuvant setting. Tumour sections were stained for p53 and HER2. p53 and HER2 scores were based on staining intensity, 2+ and 3+ being considered HER2+, nuclear staining score ⩾1% being considered p53+. The material from medical records was obtained and the adequacy of adjuvant chemotherapy was assessed. The dose of anthracyclines ⩾400 mg was considered adequate and <400 mg was considered inadequate.
Results: The prevalence of protein overexpression in the tumor was 20.6% and HER2 overexpression was 26.4%. Our results suggest that patients with tumors that were positive for p53 protein, negative estrogene receptors and treated with inadequate anthracyclines dose died within shorter period of time after diagnosis (*log rank* $p = 0.016$, *log rank* $p = 0.027$, *log rank* $p = 0.013$, respectively). There were no significant correlations with HER2 overexpression and 5-year survival in this population (*log rank* $p = 0.51$). In multivariate analysis, inadequate anthracyclines dose ($p = 0.028$) was independent factor of poor outcome (Table 1).
Conclusions: The results of this study demonstrate a consistent relationship between p53 protein overexpression, negative estrogene receptor status, inadequate anthracyclines dose and worse survival of young early stage breast cancer patients. Our data do not support a significant prognostic role for HER2 overexpression in predicting survival. The independent prognostic factor is inadequate anthracyclines dose in the adjuvant setting.

Table 1. Prognostic factors in stage II breast carcinomas compared with 5-year survival

Prognostic factors	Univariate		Multivariate	
	RR (95% CI)	p	RR (95% CI)	p
p53+	3.71 (1.17–11.77)	0.026	0.67 (0.17–2.67)	0.57
Inadequate anthracyclines dose	4.54 (1.22–16.89)	0.024	5.19 (1.19–22.57)	0.028
ER-	4.68 (1.02–21.45)	0.047	4.38 (0.79–3.373)	0.091

38LBA LATE BREAKING ABSTRACT

Therapy monitoring of sorafenib effect on experimental prostate carcinomas by dynamic contrast-enhanced MRI

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Background: To investigate and quantify the effects of the multikinase inhibitor sorafenib on experimental prostate carcinomas in rats by dynamic contrast-enhanced MRI assays of endothelial permeability and tumor vascularity.
Methods and Materials: 16 Copenhagen rats implanted with subcutaneous prostate carcinoma allografts (MLLB-2) were imaged at baseline and after a one-week treatment course of sorafenib via gavage by dynamic MRI at 3.0T following enhancement with a prototype macromolecular contrast agent [albumin-(Gd-DTPA)]. Quantitative MRI estimates of tumor microvessel permeability (transfer constant K^{PS}, 10^{-3} min^{-1}) and tumor vascular richness (blood volume; %) were calculated with PMI 0.4 software based on a two-compartment kinetic model.
Results: Sorafenib significantly suppressed endothelial permeability and blood volume in prostate carcinoma allografts over the treatment course of one week. In sorafenib-treated tumors (n = 8) the transfer constant K^{PS} yielded a significant decrease in endothelial permeability from baseline to day 7 (baseline K^{PS} = 0.62±0.20, day 7 K^{PS} = 0.08±0.09; p < 0.01). The blood volume in sorafenib-treated tumors decreased significantly over the treatment course (baseline BV = 5.1±1.0, day 7 BV = 0.56±0.48; p < 0.01). In the control tumors without treatment (n = 8), neither the transfer constant nor the blood volume changed significantly.
Conclusion: Sorafenib, a known inhibitor of angiogenesis in renal and liver cancer, significantly reduced endothelial permeability and tumor vascularity in a prostate cancer model as assayed by dynamic MRI enhanced with macromolecular contrast media. Dynamic MRI enhanced with macromolecular contrast media could prove valuable for monitoring the anti-angiogenic effect of sorafenib on an individual patient basis.

39LBA LATE BREAKING ABSTRACT

Preoperative serum CA 15−3 and CEA in women with breast cancer and their relationship with relapse of the disease

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Background: The aim of this retrospective study was to investigate whether the preoperative CA 15−3 and CEA serum levels are able to predict patients who may have a shorter disease free survival interval after curative surgery in women with breast cancer (BC).
Materials and Methods: We retrospectively reviewed a series of 363 consecutive postmenopausal women (median age 63 years, range 47−89 years) with pT1−2, N0−1 BC who were followed-up for at least 36 months after lumpectomy or mastectomy. Two Groups of patients were considered: Group 1 (age 47−64 years), 203 (55.9%) patients; Group 2 (age >64 years), 160 (44.1%) patients. The greater diameter of the tumor (pT) did not differ between Groups (19.9±13.6 vs. 22.7±14.0 mm, p = 0.06), while the preoperative CA 15−3 and CEA serum levels were higher in older patients: 19.0±14.3 vs. 24.9±27.3 U/L (p = 0.01), and 2.7±8.5 vs. 4.8±11.0 ng/mL (p = 0.04), respectively.
Results: During follow-up (36−60 months) 62 (17.1%) patients developed relapse (DR) of the disease (41 and 20 among Groups 1 and 2, respectively), while 301 (82.9%) were disease-free (DF). Group 1: baseline CA 15−3 serum levels: (DF) 25.0±11.4 (DF) vs. (DR) 31.4±14.6 U/L (p = 0.003); baseline CEA serum levels: (DF) 5.9±4.8 vs. (DR) 7.4±6.4 ng/mL (p = 0.099). Group 2: baseline CA 15−3: (DF) 27.3±13.2 vs. (DR) 20.4±6.5 U/L (p = 0.023); baseline serum CEA levels: (DF) 6.6±5.2 vs. (DR) 3.7±2.5 ng/mL (p = 0.015).
Conclusions: Surprisingly, in the subgroup of older patients with relapse (DR), both CA 15−3 and CEA serum levels were lower than in the subgroup of disease-free patients (DF). We conclude that, although serum tumor markers levels should be useful during follow-up, their baseline levels are not useful in predicting relapse in elderly patients with BC.

40LBA LATE BREAKING ABSTRACT

Results of an RCT investigating the cost-effectiveness of four follow-up strategies after breast cancer

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Background: The cost-effectiveness of frequent follow-up (f-up) visits after treatment for breast cancer is debated. Therefore, we conducted a multicenter RCT (ISRCTN 74071417) to determine the costs and effects of four f-up strategies, investigating hospital f-up, nurse-led telephone f-up, and an educational group program (EGP).
Method: Between 2005 and 2008, 320 breast cancer patients were randomized into one of four f-up strategies for their first year after treatment: 1. hospital f-up; 2. nurse-led telephone f-up; 3. hospital f-up with EGP; 4. nurse-led telephone f-up with EGP. The EGP consisted of two group-sessions, led by a breast care nurse and health psychologist, in which physical and psychosocial sequelae of diagnosis and treatment were discussed.
Costs and effects of the four f-up strategies were compared to determine the most cost-effective strategy. Costs were calculated from a societal perspective, thus included healthcare costs (e.g. outpatient clinic visits, laboratory tests, diagnostic imaging), patient costs, and productivity losses. Effects were expressed as quality-adjusted life-years (QALYs), measured by the EQ-5D. Data were collected at baseline, three, six, and 12 months after treatment. Non-parametric bootstrapping with 1000 replications and one-way sensitivity analyses were used to assess the uncertainty in costs and effects.
Results: Nurse-led telephone f-up with EGP (f-up strategy 4) was the cheapest and most effective f-up strategy. Mean annual costs per patient were €3003 and this strategy yielded 0.771 QALYs. Mean annual costs per patient and mean effects for hospital f-up (f-up strategy 1) were €3603 and 0.750 QALYs. Mean costs and effects for nurse-led telephone f-up (f-up strategy 2) were €3933 and 0.766 QALYs, and for hospital f-up with EGP (f-up strategy 3) €3281 and 0.746 QALYs. Hence, in the incremental cost-effectiveness analysis, nurse-led telephone f-up with EGP dominated all other f-up strategies. Uncertainty analysis showed that the probability of this dominance ranged between 62& and 70% for different QALY threshold values. Furthermore, sensitivity analyses with a range of cost prices for hospital visits (€50−200) and telephone f-up (€10−50) showed that cost-effectiveness results were robust.
Conclusion: Nurse-led telephone f-up with an educational group program is the most cost-effective f-up strategy out of four different f-up strategies for the first year after breast cancer.

41LBA LATE BREAKING ABSTRACT

Single institute phase II study of weekly cisplatinum and metronomic dosing of endoxan and methotrexate in second line metastatic breast cancer triple-negative

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Background and Introduction: Triple negative breast cancer is a disease prevalent in developing countries and non caucasian population. There is no standardized treatment options available include using combination chemotherapy with biologics, novel drugs results of which are of limited overall survival at prohibitive costs. This study involves the use of weekly cisplatinum with metronomic dosing of cyclophosphamide and intermittant methotrexate.