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.