phosphoproteomics upon sorafenib treatment was conducted in four biological replicate experiments leading to the identification of more than 20,000 phosphorylation sites. About 700 phosphorylation sites were significantly regulated at a false discovery rate of 5%. Mapping of the regulated phosphorylation sites to signal transduction pathways revealed severe down-regulation of the MAP kinase pathway thus confirming the expected cellular inhibition of various members of the MAP kinase family. In addition, several other pathways were deregulated. In particular the mTOR pathway was significantly affected by sorafenib.
Conclusions: Systems-wide analysis of sorafenib effects in a prostate cancer cell line revealed important, yet unknown modes of action, such as a significant influence on the mTor-signalling pathway. We demonstrated that global phosphoproteome analysis provides a better understanding on how this kinase inhibitor works on a molecular level in the treatment of cancer.

28LBA LATE BREAKING ABSTRACT

Conceptual change in oncology: Progression-Free-Survival (PFS) is a more appropriate surrogate for Overall Survival (OS) than Time-To-Progression (TTP)

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Background: Time-To-Progression (TTP) and Progression-Free-Survival (PFS) are often used to approve new treatments and to support guidelines. This study describes the relationship between TTP, PFS and OS and provides a model which explains differences and important consequences for research and practice in oncology.
Methods: Data on TTP or PFS as well as on OS were extracted from randomized clinical trials published in 2007 and 2008. Linear regression of TTP and OS, PFS and OS were computed, OS being the dependent variable. Their correlation was expressed with Pearson's correlation coefficients. The frequencies of significant differences of TTP, PFS and OS were compared.
Results: 56% of the studies used TTP, 25% used PFS and 19% used other measures in addition to OS to describe the results. In some studies TTP/PFS was measured from the time of randomization and in others from begin of therapy. In some studies only tumor specific deaths were included but in others deaths of any cause. About 10% of studies claimed to measure PFS (according to the definitions of the US Dept. Health and Human Services 2000) but in fact measured TTP or vice versa. In two studies TTP was longer than survival. The correlation coefficient of TTP and OS was 0.54 (n = 163) and of PFS and OS was 0.89 (n = 75). In 26% of studies which reported TTP significant differences in OS and in 40% of cases significant differences in TTP were reported. In studies which reported PFS significant differences in PFS were reported in 45% and in OS in 17% of cases.
Discussion: PFS is defined as time to progression or death whatever comes first and considers both, structural and functional aspects. TTP is defined as time to progression where cases are censored if death occurs before progression. This means that TTP excludes the functional aspect which is included in PFS. The model predicted that the correlation of PFS and OS will be better than the correlation of TTP and OS and that the effects of most treatments which do not extend OS will be overestimated. Researchers may preferably report TTP in cancers with favourable prognosis but report PFS when the prognosis is poor. In conclusion, our model predicts and our data confirm the findings of several other studies which suggested that PFS is a better surrogate for survival then TTP. Authorized organisations should supplement the missing criteria for assessment of PFS. TTP overestimates the effects of treatment and may be used only together with PFS.

29LBA LATE BREAKING ABSTRACT

Efficacy, safety and patient acceptability of fentanyl pectin nasal spray compared with immediate-release morphine sulphate tablets in the treatment of breakthrough cancer pain: a multicentre, double-blind, double-dummy, multiple-crossover study

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Background: Breakthrough cancer pain (BTCP) affects most cancer patients; the analgesic time course of current oral therapies does not match the typical time course of BTCP. Fentanyl pectin nasal spray (FPNS) has kinetics that enable a rapid onset of pain relief (PR). The aim of this study was to assess efficacy of FPNS compared with immediate-release morphine sulphate (IRMS) in the treatment of BTCP.
Material and Methods: Patients (N = 110) experiencing 1−4 BTCP episodes/day whilst taking $\geqslant$60 mg/day of oral morphine (or equivalent) for background cancer pain entered a double-blind, double-dummy (DB/DD), multiple-crossover study. Those who completed an open-label titration phase (N = 84) continued to a DB/DD phase; 10 episodes of BTCP were randomly treated with FPNS and oral capsule placebo (5) or IRMS and nasal spray placebo (5). Pain intensity (PI; 11-point numerical scale) and PR (5-point scale) were measured at 5, 10, 15, 30, 45 and 60 min post dose. The primary endpoint was pain intensity difference from baseline at 15 min (PID_{15}) vs IRMS. Secondary endpoints included time to meaningful PR ($\geqslant$2-point PI decrease), onset of pain improvement ($\geqslant$1-point PI decrease), patient acceptability/satisfaction, safety and tolerability. By-patient and by-episode analyses were completed. Safety was evaluated by adverse events (AEs) and objective and subjective nasal assessments.
Results: FPNS significantly improved mean PID_{15} scores compared with IRMS ($P = 0.0396$; modified intent-to-treat analysis N = 79). 740 BTCP episodes were analysed (FPNS N = 372; IRMS N =D 368): 57.5% of FPNS-treated episodes showed onset of PI improvement by 5 min and 95.7% at 30 min (both $P < 0.05$ vs IRMS). Clinically meaningful PR was seen in 52.4% of episodes by 10 min ($P < 0.05$ vs IRMS). More episodes treated with FPNS vs IRMS showed a $\geqslant$1-point PR score at 5 min ($P < 0.05$) and at all points through to 30 min. Patients were 'satisfied' or 'very satisfied' with the convenience (79.8%) and ease of use (77.2%) of FPNS. Overall treatment satisfaction was high; patients were 'satisfied' or 'very satisfied' with FPNS for 81.5% of episodes compared with 71.2% treated with IRMS ($P < 0.01$). Only 4.7% of patients withdrew from titration (2.4% in DB/DD phase) due to AEs; no significant nasal effects were reported.
Conclusions: FPNS provides clinically meaningful PR and a more rapid onset of analgesia than IRMS that better matches the typical time course of a BTCP episode.

30LBA LATE BREAKING ABSTRACT

Design of 1,4-dihydropyridine derivatives for overcoming ABC-mediated transporter multidrug resistance

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Introduction: Multidrug resistance (MDR) is one of the main reasons of failure in tumor chemotherapy, as tumor cells, by increasing drug efflux, acquire resistance to many anticancer agents, which never achieve effective concentrations. Drug resistant cell lines have shown increased levels of membrane glycoprotein, named P-glycoprotein (P-gp). It is an ATP-dependent extrusion pump for drugs and physiological substrates. Studies have shown the ability of neutralizing Pgp-related MDR by some reversing agents. 1,4-Dihydropyridine (DHP) is one of the MDR reversing agents. Docking is frequently used to predict the binding orientation of drug candidates to their protein targets to predict the affinity of the molecule. Hence, docking plays an important role in the rational design of drugs. In this study, therefore, we investigate the effects of DHP derivatives on MDR.
Material and Method: The structure of reversing agents was drawn by HYPERCHEM program. Conformations of the designed compounds were optimized through semi-empirical method followed by PM3 calculation by the program HYPERCHEM. Among all energy minimal conformers, the global minimum was selected. Then the crystal of Human ABCB2 was obtained from the Protein Data Bank (PDB) server. Finally Docking calculations were carried out using AutoDock program. The DHP

derivatives were obtained by changing the lipophilic or metoxy groups on the different positions of the phenyl ring.
Results: The results showed all compounds are inserted into a hydrophobic pocket in the active site region of ABCB2. The ki values has confirmed a good hydrophobic interaction of the designed compounds. The most potent compound was found to have two Cl groups on Meta- positions of the phenyl ring. The orientation of this derivative in the active site of P-gp 3D model was examined by a docking experiment. The molecular modeling shows that the NO_2 substituent forms a hydrogen bond interaction with the H of THR318. These observations and experimental results provide a good explanation for the potent and selective activity of these compounds.
Conclusion: The interactions of DHP derivatives showed that they can be considered as possible MDR reversing agents. In order to achieve better potency, it is better to keep the main structure and alternatively change the phenyl ring with a heterocyclic ring (eg. isoxazole) and add a lipophilic group (eg. Cl) to heterocyclic ring in Ortho- or Meta- positions. We hope the results of the present study are useful for the design of more effective compounds against cancer.

31LBA LATE BREAKING ABSTRACT

β-arrestin-dependent signaling by IGF-1R regulates the Ras induced transformation of mammalian cells

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Background: The receptors tyrosine kinase (RTKs) is a related family of cell surface receptors with similar structural and functional characteristics. Among them, the insulin-like growth factor receptor (IGF-1R) is one of the most important players in cancer development. IGF-1R is responsible for the transformation and proliferation of malignant cells, in prevention of apoptosis and in maintenance of the malignant phenotype of tumor cells. IGF-1R expression is a requirement for transformation by oncogenes. Mouse embryo fibroblasts with a disruption of the IGF-IR genes (R− cells), have been found to be resistant to transformation by a variety of viral and cellular oncogenes, except v-src and a mutant of Gq13. Recently, we provide evidence that b-arrestin1, which is better known to be involved in the regulation of GPCR, serves as an adaptor to bring the oncoprotein MDM2 to the IGF-1R leading to both the ubiquitination of the receptor and activation of MAPK/ERK signaling pathway.
Here we aim to investigate whether the β-arrestins mediated signals of IGF-1R is necessary for tumor transformation.
Material and Methods: We used mouse embryonic fibroblast cells (MEF) lacking β-arrestin1 (KO cells) and control MEFs stably transfected either with H-RasV12 (MEF-Ras; KO-Ras), PyMT (MEF-MT; KO-MT) or v-Src (MEF-Src; KO-Src). The transfection efficiency was verified by Western blot. To evaluate transformation we tested the cells for proliferation under serum free conditions and the ability to form colonies during anchorage independent growth.
Results: Our results suggest that oncogenic H-Ras is unable to transform immortalized mouse embryonic fibroblasts in the absence of β-arrestin1. The direct explanation of H-Ras inability to transform cells devoid to beta-arrestin is the impaired IGF-1R signaling and insufficient activation of the PI3K/Akt and ERK pathways.
Conclusions: The present results propose a more generalized, alternative mechanism for transformation by Ras and, implicitly, another possible way for targeting Ras in tumor cells.

32LBA LATE BREAKING ABSTRACT

High level gene amplification of MYC characterizes radiation-induced angiosarcomas

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Angiosarcomas (AS) are rare vascular malignancies that arise either *de novo* as primary tumors or secondary to irradiation or less often to chronic lymph edema. The cytogenetics of angiosarcomas are poorly characterized.
We applied array-CGH as a screening method to identify and FISH to confirm recurrent alterations in 33 secondary angiosarcomas (31 tumors secondary to irradiation, 2 tumors secondary to chronic lymph edema) and compared the results with 28 primary angiosarcomas. Recurrent genetic alterations were identified only in secondary but not in primary cancers.
The most frequent alterations were high level amplifications on chromosome 8q24.21 (50%), 10p12.33 (33 %) and 5q35.3 (11 %). FISH analysis confirmed high level amplification of *c-myc* on chr. 8q24.21 as a recurrent genetic alteration found exclusively in AS secondary to irradiation or chronic lymph edema. Amplification of *c-myc* was not predisposing to high grade morphology or increased cell turn over.
In conclusion, in spite of their identical morphology, secondary AS are genetically different from primary AS and are characterized by a high frequency of high level amplifications of *c-myc*. These findings may have implications both for the diagnosis and treatment of these tumors. Therapeutics targeting MYC and MYC-dependent signalling could be of major interest.
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33LBA LATE BREAKING ABSTRACT

Synergistic augmentation of arsenic trioxide-induced cytotoxicity by BCNU through reactive oxygen species-related autophagic pathway in human solid tumors

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Background: Arsenic trioxide (ATO) is an effective cancer therapeutic drug for acute promyelocytic leukemia and has potential anticancer activity against a wide range of solid tumors. To improve therapeutic efficacy of ATO in solid tumors, we systematically investigated the combinatory interaction of this drug with other chemotherapeutic agents.
Material and Methods: Growth inhibition was determined using the methylene blue staining method and MTT assay. Two agents were combined at equitoxic ratios based on the IC_{50} of each drug. Efficacy improvement was evaluated using isobologram at 50% inhibition level. Western blot, flow cytometry, immunohistochemistry, enzymatic activity assay were used to reveal molecular events of synergistic interaction of two drugs in this study.
Results: Isobologram analysis revealed that BCNU exhibited synergistic interaction with ATO in human nasopharyngeal carcinoma (HONE-1), melanoma (A2058), glioblastoma (BBTRG-05MG), colorectal carcinoma (HT-29), gastric carcinoma (TSGH), and non-small-cell lung carcinoma (H460). Annexin-V-propidium iodide binding, caspase 3 activity, and PARP cleavage assay indicated that combined ATO with BCNU did not induce cellular apoptosis. Instead, special biological staining with acridine orange and microtubule-associated protein 1 light chain 3, revealed ATO plus BCNU resulted in an increased percentage of autophagic cell death in HONE-1 cells compared to ATO alone. Further analysed indicates that the synergistic augmentation of the cytotoxicity trough autophagic cell death by ATO with BCNU majority through the depletion of reduced glutathione followed augmentation of reactive oxygen species (ROS). Moreover, depletion of reduced glutathione is through the inhibition of catalytic activity of thioredoxin reductase and glutathione reductase.
Conclusion: Taken together, the synergistic interaction of ATO with BCNU is through ROS related-autophagic pathway. These findings will be useful in designing future clinical trial of combination chemotherapy with ATO and BCNU with a potential for a broad use against human cancers.

34LBA LATE BREAKING ABSTRACT

Activated cPLA2a correlates with HER2 over-expression and mediates estrogen-induced cell growth of breast cancer cells

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The cytosolic phospholipase A2 (cPLA2α) catalyzes the hydrolisis of membrane glycerophospholipids to release arachidonic acid, which is converted to biactive eicosanoid lipid mediators, including prostaglandins produced through cycloxigenases, promoting activation of downstream proliferative cell signaling pathways. The eicosanoid signalling pathway contributes to cell proliferation in breast cancer. Numerous studies demonstrated a crucial role of COX-2 and PGE2 in breast tumorigenesis and progression. The specific role of cPLA2α, however, is not established. Recent work from our group demonstrated that 17β-estradiol (E2) can rapidly activate cPLA2α in the breast cancer-derived MCF-7 cell line, leading to the hypothesis that the rapid release of bioactive lipids may play a role in the proliferative signalling responses stimulated by E2 in breast cancer cells. We have shown that the E2-induced rapid activation of cPLA2α was dependent on specific trans-activation of EGFR/HER2