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