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Synergistic antitumor activity of the combination of the multi-targeted tyrosine kinase inhibitor sorafenib and of EGFR inhibitors in human colon and lung cancer cell lines

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Purpose: Tumor cell survival, growth, invasion and metastasis depend on efficient tumor cell proliferation and on tumor-induced angiogenesis. Simultaneous targeting of both these pathways could provide a better anticancer therapeutic strategy. Pre-clinical studies have shown that the combination of EGFR inhibitors, such as cetuximab, a chimeric human-mouse anti-EGFR monoclonal antibody, or erlotinib, a small molecule EGFR-selective tyrosine kinase inhibitor, and of anti-angiogenic drugs results in the potentiation of anti-tumor activity. In this study, we have evaluated the efficacy of the combination of sorafenib, a multi-targeted tyrosine kinase inhibitor and cetuximab or erlotinib, which are currently used for the treatment of metastatic colorectal cancer and non small cell lung cancer (NSCLC), respectively.
Methods: The antiproliferative effects of sorafenib in combination with gefitinib or cetuximab against a panel of human lung (A549, GLC-82, Calu3, H460) and colon (GEO, HCT-15, HCT-116, HT-29, SW480) cancer cells with a functional EGFR autocrine pathway, were determined after a concurrent 5 days exposure using a soft agar anchorage-independent growth assay. Combination effects were analyzed using the isobolographic model according to the Chou and Talalay method. Cell cycle distribution and apoptosis were quantitated by flow cytometry.
Results: Treatment with sorafenib, erlotinib or cetuximab caused a dose-dependent inhibition of soft agar growth in all the nine human cancer cell lines tested. A dose-dependent synergistic effect in growth inhibition and in apoptosis was observed by the combined treatment with sorafenib and erlotinib or with sorafenib and cetuximab in all cancer cell lines. Sorafenib induced cell cycle arrest in G1, while cetuximab and erlotinib did not induce significant changes in cell cycle distribution as compared to control untreated cells. The combined treatment with sorafenib and each EGFR inhibitor induced a significant increase in the G1 phase of the cell cycle.
Conclusion: The combination of sorafenib with erlotinib or of sorafenib with cetuximab resulted in a strong antiproliferative and pro-apoptotic activity providing a rationale for the development of multi-targeted anticancer strategies.

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Genetic polymorphisms in xenobiotic-metabolizing enzymes and their association with colorectal cancer

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Background: Carcinogenesis is a complex process associated with genetic and lifestyle factors. One of the most common forms of cancer is colorectal cancer (CRC). CRC affects approximately 5% of worldwide population. More than 75% of CRC cases represent sporadic forms. Susceptibility to nonhereditary CRC is significantly influenced by polymorphisms and mutations in low-penetrance genes. Genetic polymorphisms in xenobiotic-metabolizing enzymes may result in variations in detoxification capacity and thus influence the levels of carcinogenic compounds and subsequently the risk of cancer. Therefore, we aimed to study associations of polymorphisms in genes coding biotransformation enzymes with CRC. Based on frequency in Czech population and functional effects we selected polymorphisms in CYP1B1, EPHX1, GSTM1, GSTT1, GSTP1, NQO1, SOD2 and MPO.
Materials and Methods: Through the PCR RFLP and DNA sequencing analysis we followed their prevalence in groups of 500 CRC patients and 500 controls.
Results: Statistical analysis showed: (1) The lack of association of particular polymorphisms with CRC risk in unselected population. (2) Female carriers of variant genotype in NQO1 were at significantly higher risk of CRC in comparison with those carrying normal genotype. There was no association of this polymorphism with CRC risk in males, but previously we reported its role in breast cancer in Czech and Austrian populations. (3) Age played no role as confounding factor.
Conclusions: First study of this kind on Czech population showed that polymorphisms in xenobiotic-metabolizing enzymes may present risk factors in CRC. Further study should be focused at searching for differences in exposure between genders and assessment of importance of polymorphism combinations. Identified risk modifying factors may be used for formulation of preventive and therapeutic strategies.
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Pharmacokinetic characterization of BI 2536 – a novel Plk1 inhibitor – in advanced cancer patients

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Background: BI 2536 is a novel highly potent and specific inhibitor of the serine-threonine Polo-like kinase 1 (Plk1), a key regulator of cell cycle progression. The pharmacokinetics of BI 2536 after intravenous administration was investigated in the first treatment cycle of three different dosing schedules in advanced cancer patients (Schedule 1: 60 minutes infusion on day 1; Schedule 2: 60 minutes infusion on days 1 and 8; Schedule 3: 60 minutes infusion on days 1, 2 and 3).
Methods: Sequential cohorts of 3–6 patients with advanced or metastatic solid tumours received infusions of BI 2536 following a toxicity guided dose escalation design. Dose of BI 2536 within the different schedules were: Schedule 1: 25–250 mg (39 patients); Schedule 2: 25–200 mg (42 patients); Schedule 3: 50−70 mg (20 patients). Blood samples to determine the drug plasma concentration were taken at different time points in the first treatment cycle before, during and after the infusion.
Results: BI 2536 showed no relevant deviation from dose proportionality within the maximum plasma concentration or exposure (AUC) over the dose range tested (25–250 mg). BI 2536 revealed a multi-compartmental pharmacokinetic behaviour. The plasma concentration showed a fast decline after the end of infusion indicating a very fast disposition phase, most likely representing distribution into tissue. The plasma concentration decreased within 30 minutes after end of infusion to about 1/3 of the concentration at the end of infusion. BI 2536 is a high clearance drug with only minor contribution of urinary excretion of parent compound to the total clearance. No accumulation was observed within the Schedule 2 between days 1 and 8, whereas a slight accumulation was observed in the Schedule 3 between days 1 and 3. Neutropenia as a mechanism-related toxicity indicates target inhibition in vivo. Therefore the exposure after the first infusion (Schedules 1 and 2) was correlated to the decrease in neutrophil count on day 8 (assumed nadir). In addition influence of age, weight, gender and body surface area on the exposure was investigated. For none of the covariates a relevant influence on the exposure in the range tested was observed.
Conclusion: BI 2536 showed dose proportional behaviour in the dose range 25–250 mg. No accumulation after once weekly and slight accumulation after once daily dosing was observed. BI 2536 showed a high clearance and a high distribution. There was a clear correlation between drug exposure and the degree of neutropenia induced by BI 2536. No relevant influence of the covariates tested on the pharmacokinetics was observed.

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Biological and clinical significance of fatty acid synthase overexpression in cancer

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Background: The enzyme fatty acid synthase (FAS) has been implicated in the development and progression of several human cancers and is an attractive target for cancer therapy. FAS expression is low in most normal tissues, but is elevated in prostate cancer subsets with poor prognosis. While FAS expression is androgen responsive, it persists or is reactivated in tumors after androgen ablation, and is high in 83% of lethal tumors examined at autopsy.
Materials and Methods: To investigate FAS upregulation in cancer as a therapeutic target we tested FAS antimebolite therapy on the transgenic adenocarcinoma of mouse prostate (TRAMP) model using C-75 and Orlistat. FAS expression was evaluated by immunohistochemistry of TRAMP tissues, including primary and metastatic lesions in mice of varying ages with and without treatment, FAS enzyme activity was determined by 14C-acetate incorporation into lipids as a measure of pathway activity