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In vitro comparison of the platinum (IV) drugs oxoplatin and satraplatin

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Introduction: Oxoplatin (cis-diammine-dichloro-trans-dihydroxo-platinum-(IV)) and Satraplatin (JM 216; bis-acetato-ammine-dichloro-cyclohexyl-amine-platinum(IV)) are currently developed and tested as oral anticancer platinum agents.
Material and Methods: Antitumor activity of both compounds was screened *in vitro* using MTT proliferation assays in a panel of 23 human cancer cell lines and compared to cisPlatin. In addition, selected metabolites, namely cis-diammine-tetrachloro-platinum(IV), JM 149 (cis-ammine-cyclohexylamine-dicloro-dihydroxo-platinum(IV)) and JM118 (cis-ammine-cyclohexylamine-dichloro-platinum(II) were tested. Cell viability and cell cycle distribution were assessed using propidium iodide-stained cells in flow cytometry and genome-wide gene expression was determined using Human Genome Survey Microarrays V2.0 (Applied Biosystems).
Results: IC_{50} values measured in a panel of cancer cell lines, including lines derived from colon, breast, ovary, SCLC and RCC among others, varied in the order cisPlatin < JM118 < JM149 < JM216 < Oxoplatin. Following a 15 min exposure of oxoplatin to 0.1N HCl mimicking gastric acid, the resulting platinum species revealed a more than twofold increase in cytotoxicity and was identified as cis-diammine-tetrachloro-platinum(IV). Similar results with 0.1 N HCl were obtained for JM149, however, not for the parent drug, JM216/Satraplatin. Cell cycle perturbations induced by the different platinum complexes in COLO 205 colon cancer cells included mainly arrest in G2/M, in correlation with the respective cytotoxicity observed. In comparison, Satraplatin showed highest activity in tumor cell spheroids. Genome-wide expression profiling was performed using the SCLC cell line H526 following treatment with the different platinum complexes in concentrations that yielded comparable toxicity. Whereas application of cisPlatin, Oxoplatin, Oxoplatin/HCl and Satraplatin affected different genes, Oxoplatin and JM 149, distinguished by a cyclohexylamine moiety, gave rather similar changes in the gene expression patterns.
Conclusion: Oxoplatin and Satraplatin constitute potent oral agents that form highly active metabolites depending on their formulation, which allows for activation of the former by gastric acid and of the latter in the circulation.
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Promising cytotoxic activity profile of fermented wheat germ extract (Avemar®) in human cancer cell lines

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Avemar® is a fermented wheat germ extract with potent antimetastatic, antiproliferative and immunomodulatory activities. Chemically, it is a complex mixture of biologically active molecules including 2-methoxy-p-benzoquinone and 2,6-dimethoxy-p-benzoquinone which were supposed to be responsible for the main biological properties of Avemar. Despite its ubiquitous use as nutrition supplement for cancer patients in some countries only limited data are available on its activity in human cancer or in combination with chemotherapy. Aim of this study was to investigate the potential activity of Avemar in a panel of human cancer cell lines including colon, testis, thyroid, ovary, NSCLC, breast, gastric, Head and Neck, hepatoma, glioblastoma, melanoma, cervix and neuroblastoma and to rule out antagonism with conventional chemotherapy. To asses the cytotoxic activity of a 96 h continuous drug exposure of Avemar alone or in combination with 5-FU, oxaliplatin or irinotecan the sulforhodamine B assay was used and drug interaction between Avemar and cytostatic drugs was analyzed by the method of Drewinko.
IC50 of Avemar ranged from 0.038 mg/ml to 0.7 mg/ml with a median IC50 of 0.33 mg/ml. The highest activity was found in neuroblastoma cell lines with an average IC50 of 0.042 mg/ml. Of note, the 8 colon cancer cell lines included in this screen had a very narrow IC50 range ranging from 0.3 mg/ml to 0.54 mg/ml.
Parallel drug treatment with Avemar and either 5-FU, oxaliplatin or irinotecan in colon cancer cell lines exerted additive to synergistic effects for all drugs with the highest degree of synergy found for combinations of Avemar with 5-FU. No antagonistic drug interaction was observed. Currently, the relevance of sequential treatment for drug combinations with Avemar is analyzed in colon cancer cell lines and the potential differentiating property of Avemar is investigated in testicular cancer cell lines using cellular morphology and Oct-4 protein expression as marker for differentiation.
In conclusion, Avemar posses broad spectrum preclinical antineoplastic activity and additive to synergistic drug interactions were observed for combinations with irinotecan, oxaliplatin and 5-FU in colon cancer cell lines. Further evaluation of Avemar as potential anticancer agent seems warranted. Combined treatment of colorectal cancer patients with irinotecan or oxaliplatin containing regimens and Avemar seems feasible with respect to drug interaction on the cellular level.

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Identification of altered genes associated with non-small cell lung cancer promotion and progression

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Lung cancer is the most common cause of neoplasia-related death worldwide. One of the crucial early events in carcinogenesis could be the induction of the genomic instability phenotype. We investigated genomic instability in 30 patients with non-small cell lung cancer (NSCLC). DNA from tumor and corresponding normal tissues of 30 patients with NSCLC was isolated and amplified with six arbitrary primers using arbitrarily primed polymerase chain reaction (AP-PCR). Comparing AP-PCR profiles of normal and tumor tissue qualitative (structural DNA alterations) and quantitative (chromosomal gains and losses) electrophoretic changes were detected. Selected 21 DNA bands with altered mobility were isolated from polyacrylamide (PAA) gels, cloned and sequenced. The obtained sequences were submitted to homology search in GenBank and ten genes were identified: *TSPAN14, CDH12, RDH10, CYP4Z1, KIR, E2F4, PHACTR3, PHF20, PRAME* family member and *SLC2A13* or *HMIT*. We next examined their relation to the patients' clinicopathological parameters and survival. Alterations of *TSPAN14* and *SLC2A13* appeared prevalently in tumors of grade 1, while mutations in *PHF20* and *TSPAN14* were slightly more present in tumors of stage I, suggesting that they could play a role in NSCLC promotion. Patients with altered *TSPAN14* and *PHF20* had shorter survival. Tumors of grade 3 were characterized by the presence of *CYP4Z1, KIR* and *RDH10*. Similar features had tumors of stage III with the presence of *CYP4Z1, KIR* and *CDH12*. These genes could play a role in NSCLC progression. *E2F4*, *PHACTR3* and *PRAME* family member, equally distributed among tumors of different grades and stages, most probably play important role in NSCLC geneses. Patient with altered *E2F4* and *PHACTR3* lived significantly shorter. Detected genes could show us a way for search of biomarkers that would enable the identification of subjects at risk for developing NSCLC, improve the early detection of lung cancer and help predict patient outcome and response to chemotherapy.

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Biochemical markers of bone remodeling as predictors of skeletal morbidity and outcome in patients with solid tumors metastatic to the skeleton receiving the biphosphonate zoledronic acid

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Background: Receptor Activator of Nuclear factor KappaB Ligand (RANKL) and its endogenous inhibitor osteoprotegerin (OPG) are important determinants of bone remodeling in patients with solid tumors metastatic to the skeleton. We aimed to evaluate the effect of treatment with the biphosphonate zoledronic acid on markers of bone remodeling and to detect possible correlations of marker response with skeletal morbidity and negative clinical outcomes.
Patients and Methods: Levels of the markers of bone resorption serum C- terminal cross-linked telopeptides of type I collagen (CTX), Tartrate-Resistant Acid Phosphatase type isoform 5b (TRACP 5b) and Osteopontin (OPN) and of the bone formation marker bone-specific alkaline phosphatase (bALP), as well as levels of RANKL and OPG were evaluated at the onset of skeletal metastases and six months after initiation of treatment with zoledronic acid (4 mg monthly) in 70 patients with breast (n = 30), lung (n = 20) or prostate (n = 20) cancer. Logistic regression models were applied to assess the correlation between bone marker level changes and Skeletal Related Events (SRE, primary endpoint), recurrence and death.
Results: After a median follow-up of 32 months, 34 patients (48.6%) presented with at least one SRE and 48 patients (68.6%) relapsed.