concentrations which are obtained with metronomic vinorelbine in patients. The effects on VEGF and VEGFr2 were insignificant.

Conclusion: This data provide experimental support to the rationale of metronomic dosing protocols of oral vinorelbine as a therapeutic strategy in cancer patients.

534 Poster

Mutation analysis of the genes coding for fluoropyrimidines' catabolizing enzymes in prediction of fluoropyrimidines-associated toxicity in cancer patients

Z. Kleibl[1], J. Fidlerova[1], P. Kleiblova[1], M. Bilek[2], J. Sevcik[1], J. Novotny[3]
[1]Charles University in Prague First Faculty of Medicine, Inst. of Biochemistry and Exp. Oncology, Prague, Czech Republic; [2] Charles University in Prague First Faculty of Medicine, Inst. of Forensic Medicine and Toxicology, Prague, Czech Republic; [3] Charles University in Prague First Faculty of Medicine, Dept. of Oncology, Prague, Czech Republic

Fluoropyrimidines (FPs) are widely used for therapy of GIT, breast, and H&N cancers, however, in approximately 5-15 % of patients occur symptoms of severe FPs-related toxicity (mucositis and hematological toxicity), leading to life-threatening complications in about 1% of patients. We performed mutation analysis of the genes coding for three FPs-catabolizing enzymes: dihydropyrimidine dehydrogenase (DPD), dihydropyrimidinase (HPYS) and β-ureidopropionase (BUP1) to test their influence for development of FPs-related toxicity in Czech patients.

Mutation analysis was performed on the panel of cancer patients treated by FPs-containing regimes consisting of 73 patients with severe FPs-related toxicity (grade III-IV) and 40 patients with excellent tolerance of FPs treatment. Analysis of coding sequences of DPD was performed by sequencing of DPD mRNA (cDNA), mutation analysis of HPYS and BUP1 was performed using DHPLC analysis of PCR-amplified exons. Frequencies of characterized mutations were estimated by analysis of population controls.

Nine different alterations were found in DPD. The most frequent alterations/polymorphisms C29R; K63E; M166V; S534N; I543V; F632F; V732I; E412E, were scored in 72% of patients with toxicity and 77 % patients without toxicity. These frequencies were similar to that found in population controls. Disease-predisposing mutation IVS14+1G>A (e14 skipping) was presented in 4% of toxicity patients. We have found correlation of several DPD alterations in development of site-related toxicity: the positive correlation was scored for leucopenia and V732I (OR=6.8; p=0.0036), thrombocytopenia and V732I and C29R, and negative correlation was found for mucositis and I543V.

Mutation analysis of HPYS revealed seven different genetic changes: c.-1 T>C; R481W; S5S; L35L; F72F; IVS1-58T>C and IVS4+11G>T. Similarly to DPD, the frequencies of HPYS alterations did not differed significantly between toxicity and non-toxicity patients. Analysis of exons 1 and 2 of BUP1 lead to characterization of genetic alterations –29G>A; -6C>T and previously described SNPs (42C>G; 105A>T; 4764A>G). Frequencies of all these variants are similar in both groups of patients.

Despite we have failed to found association between occurrence of DPD, HPYS and BUP1 sequence variants and development of overall FPs-associated toxicity the analysis of DPD mutations/polymorphisms can be useful for site-related toxicity prediction.

Acknowledgements: supported by IGA MZ CR 1A8708-4.

535 Poster

Nanoparticle of cholesterol-bearing pullulan as a carrier of anticancer drugs

K. Satoh[1], F. Chen[1], A. Aoyama[1], H. Date[1], K. Akiyoshi[2]
[1]Kyoto University Hospital, Department of Thoracic Surgery, Kyoto, Japan; [2] Tokyo Medical and Dental University, Institute of Biomedical and Bioengineering, Tokyo, Japan

Background: Recently, Macromolecular assembly systems of polymer amphiphiles have attracted much attention as a vehicle for drug delivery systems (DDS). Cholesterol-bearing hydrophobized pullulan (CHP) modified with amino groups (CHPNH2) is a newly developed drug delivery vehicle that can be used to formulate nanoparticles (diameter 20–30 nm) including drugs. The complexed nanoparticles thus obtained formed a very stable colloid. The purpose of this study is to investigated whether and how effectively CHPNH2 nanogel could be used as a DDS of anticancer drug.

Materials and Methods: Docetaxel (DOC) was prepared by simple mixing with CHPNH2 (CHPNH2-DOC). Cytotoxicity of DOC and CHPNH2-DOC against five non small cell lung cancer cell lines were examined by WST-1 assay. Half-maximal inhibition constants (IC50) were determined using the non-linear regression program CalcuSyn (Biosoft, Cambridge, UK).

Results: The IC50 values of CHPNH2-DOC were significantly lower than that of DOC alone. In vivo efficacy of CHPNH2-DOC and DOC were also investigated preliminarily by pleural dissemination mouse model, in which H1299 cells were implanted into the murine pleural space. Tumor growth was monitored using an in vivo imaging system. Pleural tumor cell growth treated with CHPNH2-DOC was lower than DOC alone mice, and CHPNH2-DOC also was prolonged the survival of mice inoculated with non small cell lung cancer cells.

Conclusions: These findings showed that CHPNH2-DOC can be achived stronger effect than DOC alone in vitro and in vivo. Furthermore, CHPNH2 may be a promising efficient drug delivery vehicle.

536 Poster

Synthesis and cytotoxic activity of novel imidazo[1,2-a]pyridines and quinolines

M.A. Vilchis-Reyes[1], M.A. Martinez-Urbina[1], E. Diaz Torres[1], A. Guzmán Sánchez[1]
[1]Instituto de Química UNAM, Organic Chemistry, Mexico Distrito Federal, Mexico

Cancer is a leading cause of death only after cardiovascular diseases. The incidence of cancer has not dropped over the last decades and the most complicated cases are presented in developing countries. For that reasons, it is important to develop new compounds with antitumoral activity.

In recent years, cyclin dependent kinases (CDKs) have been proposed as a plausible target against cancer. As a part of our search for new antitumoral compounds, a new series of 2-aminopyrimidines-substituted imidazo[1,2-a]pyridines and quinolines, compounds 1-6, have been synthesized and tested against the following human cell lines: U251, PC-3, K-562, HCT-15, MCF-7 and SKLU-1.

Coupling between different aryl halides and the amine group of the pyrimidine ring was successfully achieved under the Buchwald-Hartig conditions using 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene as ligand, bis(dibenzylideneacetone)palladium (0) as catalyst and cesium carbonate in toluene.

Cell viability was measured using the sulforhodamine assay.

Compounds 1-3 diminished the metabolic ability of all cell lines tested at 50 μM. Compounds 1-3 exhibited remarkable cytotoxicity in K562 and HCT-15; SKLU-1 presented 100% growth inhibition at 50 μM. The results for compounds 4-6 will be presented. The IC_{50} values for cell lines growth inhibition and the CDK inhibition of selected compounds will be shown

537 Poster

Treatment results with fermented mistletoe (Viscum album L.) extract as part of long-term supportive care in patients with primary non-metastatic colorectal carcinoma

W. Friedel[1], H. Matthes[2], P.R. Bock[3]
[1]Hospital Bad Bocklet, Internal Medicine and Oncology, Bad Kissingen, Germany; [2] Hospital Havelhoehe, Oncology Clinic, Berlin, Germany; [3] IFAG Basel AG, Institute for Applied Medical Research, Basel, Switzerland

Objectives: To evaluate efficacy and safety of a fermented mistletoe extract (Iscador®, ISC) in supportive care of surgically treated patients with primary non-metastatic colorectal carcinoma in comparison with a parallel control group without ISC.

Methods: In a multicenter, comparative, non-interventional cohort study in Germany and Switzerland, ISC was given in addition to conventional adjuvant chemo- and radiotherapy, while the control was treated with conventional therapy only. Endpoints were surrogates of quality of life and survival, adjusted to baseline, therapy regimen and other confounders.

Results: In 804 (429 ISC and 375 control) evaluable patients from 26 centers, the majority of the baseline characteristics, prognostic criteria, and therapy was sufficiently balanced between the therapy groups. After a median follow-up of 58 vs. 51 months, and a median ISC therapy duration of 52 months, significantly fewer ISC (19.1%) than control patients (48.3%) developed ADRs related to the conventional therapy ($p < 0.001$), had fewer symptoms during the therapy, mainly gastrointestinal and CNS ($p < 0.001$), and had an on average one week shorter hospitalization. ISC vs. control patients showed a longer tumor-free survival (p=0.013). 2.3% of the patients developed systemic ADRs related to ISC, and 23.3% local ADRs. Severe ISC-related ADRs or tumor enhancement were not observed.

Conclusions: The ISC-group showed significantly fewer ADRs of the conventional therapy, fewer disease- and therapy-related symptoms, and longer tumor-free survival than the parallel control group without ISC. The ISC-treatment was well tolerated and appears beneficial in supportive care in primary non-metastatic colorectal carcinoma.