NT analog was shown to exert minor effects on proliferation of the cancer cell lines in MTT assays. The NT analog stimulated Na^+- and amiloride-sensitive proton flux of the Na^+/H^+-exchanger 1 (NHE1). Activity of NHE1 is regulated by phosphorylation and, ERK1/2, p38α MAPK and mitogen- and stress-activated kinase1/2 (MSK1/2) were identified as responsible kinases in phosphoprotein arrays. Functional involvement of these kinases was proved with inhibitors PD 98059, SC68376 and dimethyl fumarate (DMF), respectively. Downstream targets of are MSK1/2 are CREB and NFκB and DMF was reported to inhibit metastasis of melanoma cells in experimental animals. In BxPC-3 and PANC-1 cells, lys-ψ-lys-NT(8−13) enhanced the production of IL-8, an important inducer of tumor cell dissemination, and these cells were acquired the ability to evade from an extracellular matrix gels. The NT analog upregulated expression of genes encoding cytoskeletal and adhesion proteins, glycolytic enzymes and metalloproteinases.

Conclusion. In conclusion, NT stimulated the aggressiveness of pancreatic cancer cells by induction of intracellular alkalinisation/extracellular acidosis and increased production of IL-8, in addition to its minor growth promoting effects.

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1111 POSTER

Pharmacogenetics of peripheral neuropathy in elderly patients (>65years) with advanced gastric cancer receiving oxaliplatin based chemotherapy within a randomized phase II study

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Background: Peripheral neuropathy (PNP) is a dose-limiting side effect of oxaliplatin based chemotherapy. High grade PNP may compromise quality of life especially in elderly patients (pts). A randomized multicenter phase II study was conducted to compare fluorouracil, leucovorin, oxaliplatin with or without docetaxel (FLO vs. FLOT, respectively) in elderly pts with advanced gastric cancer (AGC). Our purpose was to identify pharmacogenetic markers as predictors of high grade PNP within this study.
Methods: 143 pts were enrolled in this study. Pts. were numerically >65 years or numerically >59 years but classified biologically >65 years as defined by an *Instrumental Activities of Daily Living* score of <8. PNP was classified according to an oxaliplatin specific scale. Genotyping was performed using PCR-based RFLP or TaqMan®-based allelic discrimination. 20 polymorphisms in 13 genes being part of the metabolism of the applied drugs or DNA repair were analyzed. Statistical analyses were based on stepwise multivariate cox regression models and included genotypes and clinical parameters.
Results: Median age was 71 years (range 60−83). Pts received in median 6 cycles of treatment (range 1−12). 130 pts were evaluable for PN at time of analyses. Of these, 68 received FLO and 62 received FLOT. Cumulative grade 3 PNP occurred in 49% of pts without a significant difference between FLO and FLOT receiving pts (44% and 53%, respectively, $p = 0.4$). Genotypes of TS and MTHFR could be identified as independent risk factors for grade 3 PNP by multivariate analyses. Pts carrying a TS promoter genotype known to be associated with low TS expression (2R/2R, 2R/3RC, 3RC/3RC) were at higher risk for developing grade 3 PNP compared to pts without one of these genotypes (OR 3.0 [95%CI 1.27; 7.06], $p = 0.01$). Pts carrying MTHFR1298AC or CC genotypes were also at higher risk for experiencing grade 3 PNP compared to pts with the wildtype MTHFR-1298AA genotype (OR 3.1 [95%CI 1.26; 7.60], $p = 0.01$). In fact, 89% of pts that experienced grade 3 PNP were carriers of at least one of these risk genotypes.
Conclusion: Polymorphisms of TS and MTHFR might be associated with grade 3 PNP in AGC pts receiving oxaliplatin based chemotherapy.

1112 POSTER

The effect of adjuvant chemotherapy with a taxane and a bisphosphonate on bone mass and bone strength in an animal model

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Background: Taxane-containing chemotherapy is becoming a standard in the treatment for many different tumors such as breast cancer. The purpose of the present animal study was to investigate the direct effects of docetaxel as a modern chemotherapy agent on bone strength and bone imaging parameters and wether a bisphosphonate in an osteoporosis equivalent dose mitigates the putative effects of the chemotherapy on bone.
Materials and Methods: 45 female Sprague-Dawley rats were randomized to three experimental groups. All groups underwent a sham ovariectomy. The first group received a placebo treatment with saline injections subcutaneous while the second and third group (each n = 15) were treated with 6 cycles of docetaxel in a 3 week term. One chemotherapy group received in addition daily subcutaneous application of 1 μg/kg ibandronate while the second group received a placebo treatment.
Following methods were used in order to characterize the effects of the different treatments on bone mass and strength: Peripheral Quantitative Computer Tomography (pQCT) bone density scans and structural analysis (μCT) scans were performed at the center of the femoral neck and shaft. After bone density and structural analysis the right femora were tested in 3 point-bending, while the left femora were tested in compression mode of the femoral neck. For both tests the load displacement curve was analyzed for stiffness and ultimate load.
Analysis of the vertebral bodies included μCT and a compression test of LVB 5.
Results: 6 cycles of taxane-containing chemotherapy caused a significant decrease in almost all parameters determining bone mass and bone strength. The effects followed the same pattern in all used methods. The treatment with ibandronate was able to preserve those parameters significantly compared to the negative effects in the group treated with chemotherapy only.
Conclusion: Since hypogonadism is not the result of the treatment with docetaxel it is likely that a direct negative effect on bone is the reason for decreased bone mass and bone strength. Estrogen might even protect the bone from more devastating destruction due to chemotherapy. Further experimental investigations are underway to clarify the protective role of estrogen in cancer treatment. Furthermore, we were able to show that an osteoporosis equivalent dose of the bisphosphonate ibandronate is able to mitigate the negative effects of chemotherapy in the animal model used.

1113 POSTER

Correlation of Sodium Iodide Symporter (NIS) and Retinoic Acid Receptor Alpha (RARA) expression in breast cancer

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Background: Sodium Iodide Symporter (NIS) expression in the thyroid gland supports imaging and treatment of thyroid disease using radioactive iodide. NIS expression also occurs in malignant breast tissue suggesting potential for radioiodide in breast cancer imaging and therapy. Both in vitro and in vivo animal studies have shown that NIS expression in breast cancer is regulated by retinoic acid.
Aim: The aim of this study was to quantify NIS and retinoic acid receptor-a (RARA) gene expression in normal, benign and malignant breast tissue using RQ-PCR, and to correlate levels with clinicopathological details.
Method: Breast tissue specimens (n = 92) harvested at surgery were homogenised and RNA extracted using the Qiagen RNeasy Mini Kit. Following Nanodrop RNA quantification and reverse transcription, the corresponding cDNA was interrogated for NIS and RARA expression using RQ-PCR. To determine relative quantification (RQ) values, levels of NIS and RARA expression were normalised using the average levels of endogenous control genes PPIA and MRPL19, and expressed relative to the lowest detectable level for correlation of data. To compare individual breast cancer subtypes, results were expressed relative to levels detected in normal breast tissue. Statistical significance was analysed using the Student t test and correlation between NIS and RARA was determined using the Pearson Correlation Coefficient.
Results: NIS expression was detected in 74/76 breast cancer tissues analysed (Mean ±SEM, 1.17 ± 0.06 $\log_{10}$ RQ). There was a significant positive correlation between NIS and RARA expression in all breast tissues samples (Pearson correlation coefficient = 0.215, $p < 0.05$). The highest