Here, we combined biomarker studies from several phase III trials with bevacizumab to systematically assess whether genetic variation in VEGFA pathway genes and other genes is associated with bevacizumab-induced hypertension.
Methods: Germline DNA was available from 628 patients diagnosed with advanced primary colorectal (NO16966), pancreatic (AVITA), non-small cell lung (AVAiL), renal (AVOREN) and breast (AVADO) cancer and treated with bevacizumab. Toxicities were identified from clinical trial reports and graded according to common toxicity criteria. Overall, 113 patients had grade 1−4 bevacizumab-induced hypertension (assessed across trials with CTCAE v2−3). A total of 158 single nucleotide polymorphisms (SNPs) located in VEGFA, VEGFA-receptors (FLT1 and KDR) and other genes were selected using a SNP tagging approach and genotyped using MALDI-TOF mass spectrometry. A logistic regression on individual patient data was performed after stratification for cancer type and other covariates.
Results: Ten SNPs were associated with bevacizumab-induced hypertension ($p < 0.05$), but none of these surpassed the threshold for multiple testing ($p < 0.0003$). The three SNPs showing the strongest association ($p < 0.01$) were: rs2305949 in KDR (allelic OR 0.93, 95% CI 0.88–0.98, $p = 0.0059$), rs4444903 in EGF (allelic OR 1.06, 95% CI 1.02–1.11, $p = 0.006$); and rs1680695 in EGLN3 (allelic OR 1.07, 95% CI, 1.02–1.12, $p = 0.008$). Interestingly, rs2305949 and rs4444903 were closely linked to amino acid changes occurring on position 273 and 708 of KDR and EGF, suggesting that these changes may functionally affect both genes and thereby contribute to hypertension. Notably, rs11064560 in WNK1 was also associated with bevacizumab-induced hypertension (allelic OR 1.06, 95% CI 1.01–1.11, $p = 0.02$), thereby supporting previous observations in a limited number of patients [Frey et al. ASCO 2008].ents [Frey et al. ASCO 2008].
Conclusions: Our study represents a large genetic analysis of bevacizumab-induced hypertension using pooled data sets. The genes described warrant further investigation for their potential role in the safety profile of bevacizumab.

1413 POSTER

Expression Analysis and Study of BCL2 and the Novel Member of the Apoptotic Genes BCL2L12, as Promising Biomarkers for Monitoring of Prostate Cancer Cells' Response to Chemotherapy

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Background: Cancer continues to constitute a global public health problem. Chemotherapy is an effective approach for combating this complicated disease; however there is an urgent need of biomarkers for monitoring patients' response to it. *BCL2* gene family members, including the novel *BCL2L12* discovered from members of our research group, are known to be extensively implicated in apoptosis and their aberrant expression has been correlated with cancer progression.
Materials and Methods: The present study aims to reveal any apparent modulations in the mRNA levels of apoptotic genes belonging to the *BCL2* apoptotic gene family, including the recently identified member *BCL2L12*, upon treatment with broadly used chemotherapeutic agents. Any apparent modulations of these genes could reveal their potential role in monitoring chemotherapy response in human malignancies.
The cytostatic action of each drug was evaluated in PC3 and DU145 prostate human cancer cell lines under study, employing the MTT and trypan blue assays. Total RNA was isolated from control and treated with appropriately selected anticancer drug concentrations cells and 2 μg of it were reverse transcribed into cDNA. The expression levels of the genes under study were determined using conventional and Real-Time PCR, employing proper housekeeping genes for normalization.
Results: Increased concentrations and exposure time of the administered chemotherapeutic compounds lead to the reduction of cancer cells' proliferation efficiency. Moreover, important modulations occurred in the mRNA levels of the genes under study, fact that implicates them in distinct biochemical pathways induced upon administration of various anticancer compounds in malignant cells.
Conclusion: Our results could help towards identifying molecules which take part in the response of cancer cells to chemotherapy and could provide valuable information about the potential of novel genes that encode parts of the apoptotic machinery as valuable tools in monitoring cancer patients' response to chemotherapy, ultimately leading to more focused anticancer treatment strategies.
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1414 POSTER

Single Nucleotide Polymorphism Analysis and Outcome in Advanced-stage Cancer Patients Treated With Bevacizumab

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Background: There are no validated biomarkers predicting benefit from bevacizumab (bev) therapy. In an effort to identify such markers, biomarker studies have been integrated into several Phase III trials with bev in an attempt to correlate genetic variability in VEGFA pathway genes with the therapeutic efficacy of bev.
Methods: Germline DNA was available from 1346 subjects diagnosed with advanced primary colorectal (NO16966), pancreatic (AVITA), non-small cell lung (AVAiL), renal (AVOREN) and breast (AVADO) cancer. Overall, 628 subjects received bev. Common single nucleotide polymorphisms (SNPs) located in the hypoxia-inducible factors (HIF-1A and EPAS1), VEGFA, VEGFA-receptors (VEGFR1 and VEGFR2) and several other genes were selected using a SNP tagging approach. A total of 158 SNPs were genotyped using MALDI-TOF mass spectrometry. A meta-analysis of individual patient (pt) data was performed, after stratification for cancer type and other covariates. Genetic associations were assessed using Cox Proportional Hazard Regression for progression-free survival (PFS) and overall survival (OS).
Results: The rs4145836 SNP in EPAS1 was most significantly associated with improved PFS in both bev-treated pts (allelic HR 0.68, 95% CI 0.56–0.82, $p = 0.0001$) and placebo pts, suggesting that this SNP may be a prognostic marker for outcome independent of bev. The rs699946 SNP, located in the VEGFA promoter, was associated with improved PFS in bev-treated subjects with an allelic HR of 1.27 (95% CI 1.08–1.49, $p = 0.003$). No effect was seen in placebo subjects, suggesting that rs699946 may be a predictive marker for favourable outcome with bev treatment. The nearby rs699947 SNP in VEGFA, which has previously been associated with bev treatment outcome in breast cancer [Schneider et al. 2008], was not associated with a PFS advantage in our study. In terms of OS, the rs12505758 SNP in VEGFR2 was most significantly associated with improved OS in bev-treated pts (allelic HR 1.50, 95% CI 1.21–1.85, $p = 0.0002$). No effects for rs12505758 were seen in placebo pts.
Conclusions: Our study represents a large genetic analysis of SNPs in correlation to bev outcome, based on pooled data sets. The observed associations suggest certain genetic loci as potential markers for favourable prognosis, regardless of bev treatment, and prediction of benefit from bev. Further studies will be necessary to assess the potential clinical value of these preliminary associations.

1415 POSTER

Blood Plasma VEGFA Analysis in the AVAGAST Randomized Study of First-line Bevacizumab (bev) + Capecitabine/Cisplatin (cape/cis) in Patients (pts) With Advanced Gastric Cancer (AGC)

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Background: Recent data suggested that high plasma VEGFA (pVEGFA) levels might predict progression-free survival (PFS) benefit in bev-treated pts with metastatic breast cancer (mBC) [AVADO study, Miles et al. SABCS 2010]. Current data in lung, renal, and colorectal cancer indicate a more prognostic than predictive role for pVEGFA [Bernaards et al. ASCO 2010]. The AVAGAST study included prospective evaluation of pVEGFA as a biomarker (BM).