2) to evaluate the effects of sequence of administration on efficacy. The mean time to endpoint (TTE), defined as tumor volume =1000 mm^3, of untreated control animals was 25.4 days. The mean TTE of bortezomib (33.9 days) or SB-743921 (48.6 days) administered as a single agent at MTD did not differ significantly from untreated controls. Administration of SB-743921 24 hours prior to bortezomib resulted in a TTE of 58 days, which was superior to untreated control ($p = 0.004$) or SB743921 alone ($p = 0.038$) and comparable to activity of paclitaxel (TTE=59 days). In order to evaluate the effects of sequence of administration of bortezomib and SB-743921, the dose of SB743921 was lowered to accommodate all schedules. The combination had activity that was superior to bortezomib monotherapy when dosed simultaneously or with SB743921 first. Dosing of bortezomib prior to SB743921 was not significantly different from either monotherapy. The anti-tumor activity of the combination suggests that exploration is warranted in disease settings where bortezomib is approved.

379 POSTER

The role of Src-family kinases in the activation of the EGFR following chemotherapy

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Human cancer cells may respond to chemotherapy by activating the EGFR and survival pathways such as Akt. We have shown recently that colorectal cancer (CRC) and non-small cell lung carcinoma (NSCLC) cells that respond to chemotherapy by up-regulating phospho-EGFR, are sensitized to EGFR-targeted tyrosine kinase inhibition. We investigated the mechanism of EGFR activation following chemotherapy treatment in LoVo and HCT116-$p53^{+/+}$ CRC and H460 NSCLC cells. Following treatment with chemotherapy (antimetabolites/Topoisomerase-1 inhibitors/platinum compounds/taxanes), we found that increased phospho-EGFR was associated with increased Src-family kinase (SFK) activity. Using the SFK inhibitor PP2 and the broad-spectrum (MMP) matrix-metalloprotease and ADAM (a desintegrin and metalloprotease) inhibitor GM6001, we showed that chemotherapy-activated EGFR phosphorylation was abolished. Furthermore, we found that GM6001 had no effect on SFK activity, indicating that SFK's act upstream of metalloproteases. In addition, when PP2 or GM6001 were combined with chemotherapy, we found an additive or synergistic interaction in these cell lines. Further studies indicated that ADAM-17 and TGF-α were important regulators of chemotherapy-induced EGFR activity in the CRC and NSCLC cells. Our findings indicate that increased EGFR activity following chemotherapy is induced via SFK-mediated activation of ADAM-17, which induces shedding of TGF-α. Moreover, targeting SFK or metalloproteases in combination with existing chemotherapies may have therapeutic potential for the treatment of CRC and NSCLC tumours.

380 POSTER

Glut1 antibodies decrease proliferation and enhance the induction of apoptosis in human non small cell lung cancer (NSCLC) and breast cancer (BC) cell lines

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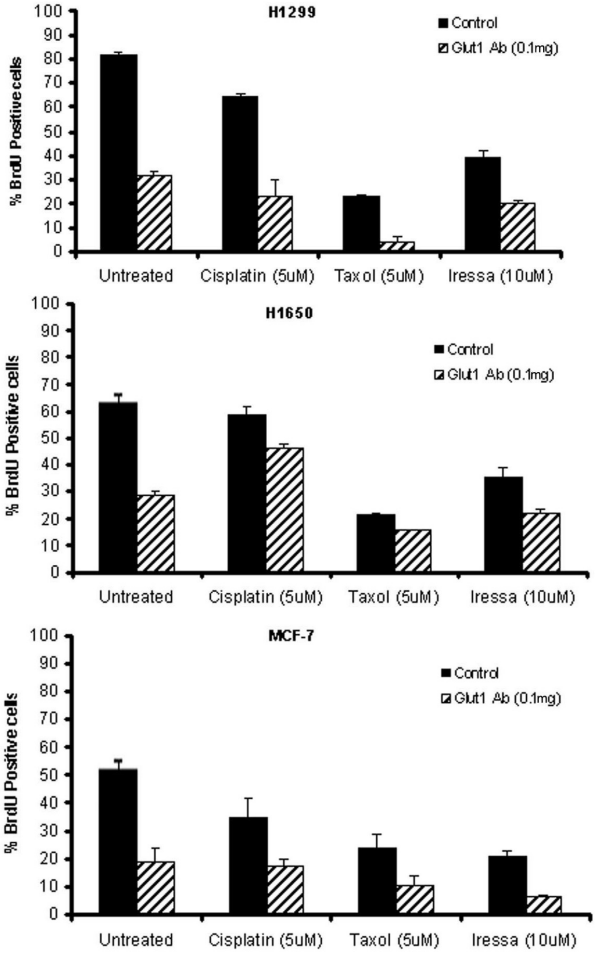
Background: A tumors' malignant potential is determined by its ability to generate energy and survive in hypoxic and acidotic environments by switching to anaerobic glycolysis. Anerobic glycolysis is an inefficient method of breaking down glucose for energy necessitating increased glucose uptake, which is facilitated by the membranous translocation of a high affinity Glucose Transporter, Glut-1. Glut-1 belongs to a family of trans-membrane glucose transporters, Glut-1−12, and is preferentially up regulated by tumors, presumably because it is a high affinity glucose transporter. We therefore hypothesized that blocking membranous Glut-1 by an anti-Glut-1 antibody would abrogate tumor growth.
Materials and Methods: BC and NSCLC cell lines were first assessed for increased Glut-1 expression. NSCLC cell lines H1260 and H1650 and BC cell line MCF7 were plated on chamber slides and incubated in presence of 5 μM cisplatin, 5 μM paclitaxel or 10 μM geftinib in absence or presence of 0.1 mg/ml anti-Glut-1 antibody. Proliferation was assessed by BrdU. Apoptosis was assessed by TUNEL Assay and PARP cleavage.
Results: In the H1299 NSCLC line treatment with the anti-Glut-1 antibody alone, inhibited proliferation by 62%, when added to cisplatin, paclitaxel and gefitinib it enhanced inhibition of proliferation by 62%, 74% and 42%, respectively. Similarly in the H1650 NSCLC cell line, treatment with anti-Glut-1 antibody alone inhibited proliferation by 55%; when added to cisplatin, paclitaxel and gefitinib it enhanced inhibition of proliferation by 18%; 23% and 46%, respectively. In the MCF7 NSCLC cell line, anti-Glut-1 antibody alone inhibited proliferation by 59%, when added to cisplatin, paclitaxel and gefitinib it enhanced inhibition of proliferation by 40%, 47% and 59%, respectively. Please see attached figure. Apoptosis was assessed after treatment with 5 μM cisplatin, 5 μM paclitaxel or 10 μM geftinib alone, and with anti-Glut-1 antibodies. Glut-1 antibodies enhanced the apoptotic effects of cisplatin, paclitaxel and gefitinib in H1650 cell line by 43%, 62% and 111%; in H1299 by 111%, 30% and 71% and in MCF7 cell line by 37%, 91% and 133%, respectively.



Conclusions: Our results indicate that anti-Glut-1 antibodies inhibit proliferation and enhance the inhibition of proliferation and apoptosis induced by cisplatin, paclitaxel and gefitinib in the evaluated NSCLC and BC cell lines, providing evidence that the use of antibodies to Glut-1 may be a viable therapeutic strategy in tumors that over express Glut-1.

381 POSTER

HSP27 as a novel target in Non-small cell lung cancer with particular implications for migration and metastasis

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Purpose: The role of HSP27 in non-small cell lung cancer (NSCLC) was evaluated with a focus on expression in metastases versus primary tumor and its role in-vitro in cell motility and migration.
Methods: Tumor tissue microarrays (TMA) were stained for HSP27 and Phospho-HSP27 (IHC) and results correlated with outcome and stage. Expression in 27 metastases was compared with the respective matched primary tumors. Cell motility in HSP27 lentivirus transfected A549 NSCLC