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tioning was as follows: schedule a) 7.86 ± 1.61; b) 5.63 ± 0.44; c) 4.82 ± 0.35; d) 5.07 ± 0.32; e) 4.62 ± 0.37, and f) 4.44 ± 0.39; while in C225-treated mice, V=100 was as follows: a) 14.28 ± 1.73; b) 15.16 ± 3.61; c) 16.94 ± 2.80; d) 11.30 ± 1.13; e) 13.93 ± 1.59, and f) 13.49 ± 1.77. Delays in time to V=100 mm^3, as well as to V=500 mm^3 and V=1000 mm^3 (data not showed), were significant (p=0.001) in all C225-treated mice, regardless of in vitro conditioning. In tumors measuring 1000 mm^3, no differences in MVD were seen in any of the groups analyzed. However, preliminary analysis of tumors whose volume was 100 mm^3 and which were derived from irradiated cells showed a lower MVD in C225-treated mice compared to saline-treated mice (39.47 ± 3.04 versus 27.80 ± 2.29; p= 0.031).
Conclusions: In this in vivo model, C225 demonstrated a high activity against radiation-resistant A431 cells. This preclinical study supports the evaluation of adjuvant treatment with C225 after radiotherapy in EGFR-dependent tumors.

1427 poster

RADIOSENSITIZING AND GROWTH INHIBITORY EFFECTS OF THE PTP1B INHIBITOR SURAMIN IN FADU CELLS

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Purpose: PTP1B acts as a key insulin receptor and leptin receptor phosphatase, and is required for normal rates of EGFR and PDGFR dephosphorylation in fibroblasts. PTP1B is also proposed to influence the Ras/ERK pathway. The purpose of this study was to investigate the role of PTP1B in modulating radiation-stimulated membrane receptor activities in K-Ras wild-type and mutated cells.
Materials: Wildtype and K-Ras mutated FaDu cells, as well as A549 cells have been treated with suramin (0.1, 0.5, 1.0 mM) every 3 days, and counted for determination of proliferation rates. Western Blot analysis of PTP1B expression as well as total and phosphorylated EGFR and AKT have been performed after different time periods (6, 18, 24 h) of treatment with suramin (0.1, 0.5, 1.0 mM) alone and in combination with EGF, TGF-α and insulin. To investigate radiosensitizing properties of the PTP1B inhibitor cells were pretreated with suramin (0.05, 0.1, 0.2 mM) prior to irradiation with single doses (1, 2, 4, or 6 Gy) and twice during colony formation assay. Surviving fractions were determined after 10 days.
Results: Treatment with suramin led to a dose dependent growth inhibition in A549 and FaDu cells. However, both FaDu wildtype and K-Ras mutated cells displayed a strikingly higher sensitivity towards suramin compared to A549 cells. Time- and concentration dependent phosphorylation of EGFR and AKT after suramin treatment alone and in combination with EGF stimulation was detected by Western Immunoblotting in A549 cells. However, insulin induced phosphorylation was reduced by suramin treatment. In EGF stimulated FaDu cells phosphorylation of EGFR was strikingly higher after suramin treatment, and was accompanied by phosphorylation of AKT. Interestingly, the amount of total EGFR was reduced with increasing suramin concentration. This was observed after treatment with EGF, TGF-α, and insulin. Radiation response i.e. clonogenic cell survival of A549 and FaDu cells was differentially affected by suramin.
Conclusions: Treatment with the PTP1B inhibtor suramin affected radiation response differentially in a concentration-dependent manner in FaDu and A549 cells. The observed increase in tyrosine phosphorylation of EGFR after suramin treatment alone and particularly in combination with EGF stimulation, resulting in activation of the PI3K/AKT pathway, most likely can be explained with the inhibitory effect of suramin on dephosphorylating activity of PTP1B. To confirm this, more specific PTP1B inhibitors are under investigation.

1428 poster

RADIOTHERAPY IN COMBINATION WITH SORAFENIB - A SUCCESSFUL TREATMENT OF BRAINMETASTASES FROM RENAL CELL CARCINOMA.

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Purpose: We report a single case of radiotherapy for brainmetastases from renal cell cancer (RCC). The patient is his own control since his first metastasis was irradiated before sorafenib was available and his second developed during sorafenib treatment. Still he responded with a complete remission after treatment with only 2 Gy fractions to 20 Gy.
Materials: Our patient is a 51 years old man who in January 2005 was diagnosed with RCC stage IV. A nephrectomy was done but no systemic treatment was given due to stable disease. In October a metastasis in the third ventricle was diagnosed. He was treated with external beam irradiation with a three field technique using a 2 cm margin and with 3 Gy fractions to 30 Gy. He responded with stable disease. After three months of interferon treatment a slight regression was seen. Due to progression elsewhere the patient started treatment with sorafenib in October 2006. At the first evaluation three months later his first metastasis had regressed and showed no contrast enhancement. However a new lesion 2.5x3cm lateral from the right lateral ventricle had developed while other metstatic sites had responded very well. Due to partly overlapping targets we could now only treat him with 2 Gy fractions to 20 Gy. Sorafenib was stopped three days before irradiation until three days after.
Results: Two months after the radiotherapy a CT scan showed a complete remission with a small area with low attenuation without contrast enhancement. The following CTs showed some contrast enhancement in the area making it difficult to distinguish between recurrence or necrosis. The latest CT from February 2008 shows however calcifications in the area indicating a healing process. Treatment plans as well as consecutive CTs will be shown.
Conclusions: The development of a new brainmetastasis during sorafenib treatment while other metastatic sites responded very well was probably caused by a lower concentration of sorafenib in the brain compaired to other parts of the body. The first metastasis in the third ventricle was in vicinity to the vascular plexus and might therfore have been exposed to a higher concentration of sorafenib. Animal studies have shown a potentiating effect of antiangiogenic agents given prior to radiotherapy by improving tumor oxygenation. Concomitant treatment has been less successful compaired to sequential treatment maybe due to cellcycle effects while sequential treatment might have a potentiating effect by inhibiting endothelial repair. A total dose of 20 Gy given with 2 Gy fractions would have no effect at all on a RCC metastsis. Our case is very illustrative and suggests that studies combining sorafenib with radiotherapy should be designed with a pretreatment followed by a stop of treatment during the radiotherapy and a restart of dosing post-irradiation.

Radiobiology : DNA repair

1429 poster

EFFECT OF N- ACETYLCYSTEINE ON RADIATION-INDUCED GENOTOXICITY AND CYTOTOXICITY IN RAT BONE MARROW

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Purpose: The aim of our study was to evaluate the potential radioprotective effects of N-acetyly cysteine (NAC) against genotoxicity and cytotoxicity and to compare its effect with that of WR-2721 (amifostine) using the chromosomal aberration (CA) and micronucleus (MN) test systems in the oxidative damage caused by gamma-irradiation in rat's tibial bone marrow cells. In addition to these test systems, we also investigated the mitotic index (MI), and the ratio of polychromatic erythrocytes (PCEs) to normochromatic erythrocytes (NCEs).
Materials: The rats (n=16) were divided randomly and equally into four groups: Control (C, received 2.2 ml saline), Radiation (R, received irradiation and 2.2 ml saline), R+NAC (received irradiation and 1000 mg/kg NAC) and R+WR-2721 (received irradiation and 200 mg/kg WR-2721) rats. All groups of rats in the study (R, R+NAC and R+WR-2721) received whole-body gamma irradiation as a single dose of 6 Gy. R rats received 2.2 ml of saline (i.p.) while the R+NAC and R+WR-2721 rats received 1000 mg/kg, (i.p.) NAC and 200 mg/kg, (i.p.) WR-2721 respectively.
Results: The rats, exposed to gamma radiation alone (group R), showed higher CA and frequency of MN formation when compared to control, as expected ($p < 0.05$ and $p < 0.01$, respectively). Group R showed higher frequency of CA (P=NS) and MN formation when compared to both R+NAC and R+WR-2721 ($p < 0.05$ and $p < 0.05$, respectively). In addition to the results obtained by irradiation alone, the mean of the group showed lower MI and PCE/NCE ratios when compared to control ($p < 0.001$ and $p < 0.001$, respectively). Moreover, the mean of both R+NAC and R+WR-2721 groups showed lower MI and PCE/NCE ratios when compared to control ($p < 0.001$, $p < 0.001$ and $p < 0.001$, $p < 0.001$, respectively). In addition, group R showed lower MI when compared to both R+NAC and R+WR-2721 groups ($p < 0.001$, $p < 0.01$ respectively).
Conclusions: Our results indicate the beneficial effects of NAC against RT-induced genotoxicity and cytotoxicity in rat bone marrow, which is a similar effect that may be comparable to that observed for WR-2721. In spite of WR-2721, NAC has not been used clinically for this purpose yet; further experimental studies are needed to prove this result and to rule out potential protection of tumor cells and to exploit the clinical advantage of NAC.