tumour control dose 50% (TCD50) were calculated and compared with the TCD50 values of the parental FaDu line after the same irradiation schedule.

Results: The TCD50 values after single dose irradiation were 37 Gy [95% CI 33;42], 39 Gy [33;43], 37 Gy [35;40] and 38 Gy [35;41] for FaDu-R1, FaDu-R2, FaDu-R3 and the parental FaDu, respectively. All investigated retransplanted recurrences showed a clear-cut time factor, i.e. TCD50 values after 18 fractions within 36 days were significantly higher than after 18 fractions within 18 days. The comparison of TCD50 values after the same overall treatment time revealed no significant differences between R1, R2, R3 and the parental FaDu line indicating an identical magnitude of the time factor in the retransplanted recurrences and in the original FaDu.

Conclusion: A genetically stable selection of rapidly proliferating clonogenic cells does not contribute to accelerated repopulation in poorly differentiated FaDu hSCC in nude mice.

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746 POSTER

Effect of recombinant human Keratinocyte Growth Factor (rhKGF) on proliferation, clonogenic capacity, and radiation response of human epithelial tumor cells in vitro

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Purpose: A fatal consequence of breaks in radiotherapy of head and neck cancer caused by severe mucositis may be a significant decrease in local control and cure. Amelioration of the mucosal response aiming at avoiding breaks could increase the therapeutic ratio of radiotherapy. Keratinocyte growth factor has been identified to ameliorate the acute response to radiation in animal models. The application of KGF in tumor treatment should not protect tumor cells. The purpose of this study is to investigate the in vitro effect of rhKGF on proliferation, clonogenic capacity, and radiation response of low passage human epithelial tumor cells in media containing low FCS concentration.

Material and Methods: Five tumor cell cultures derived from head and neck squamous cell carcinomas, three cultures derived from pleural effusions of lung carcinomas and normal nasal epithelial cells were analyzed. For experiments, cells in passage 2-6 were incubated with rhKGF (10;200 ng/ml) immediately after plating for clonal growth in serum-depleted media. To determine cellular radiosensitivity single doses of 1;8 Gy of X-rays were applied. Colony formation as well as the number of cell doublings was determined after 10;14 days of growth in rhKGF-treated and control cells. Each experiment was repeated twice, radiation survival curves were fitted by the linear-quadratic equation, and statistical comparison was preformed betweeen rhKGF-treated and non-treated cultures.

Results: Normal epithelial cells showed a two- to three-fold increase in the number of cell doublings due to KGF-treatment ($P < 0.0001$). In contrast, in tumor cell cultures only slight, not significant stimulation of proliferation occurred in 2 out of 8 samples ($P = 0.20$ and 0.07, respectively). This stimulation was abolished either by serum addition to the medium or in irradiated cells. In the remaining tumor cell cultures, which were not growth stimulated by KGF neither radiation-induced impairment of proliferation nor clonogenic cell survival was influenced by the addition of KGF to the medium.

Conclusion: A clinical pilot study indicate that KGF is well tolerated and effective in humans. In animal models, KGF has been shown to ameliorate the radiation tolerance of normal epithelia. Together with the minimum in vitro tumor cell response to KGF, compared to normal epithelial cells in this study, these results suggest a potential for selective protection of normal epithelia during clinical radiotherapy.

747 POSTER

The cytotoxicity of Ukrain does not involve the TP53/p21/p27-signal transduction cascade

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Purpose: Ukrain, a Chelidonium majus L.-Alkaloid/Thio-TEPA derivative, has shown cytotoxicity in vitro and in vivo. The mechanism responsible remains to be elusive. In this study the influence of Ukrain and ionizing radiation on the TP53-p21 pathway and the cell-cycle was investigated in human wild-type (wt) TP53 lung carcinoma cells (A549), TP53-overexpressing glioblastoma cells (U138MG) and normal wt-TP53 fibroblasts (HSF1).

Materials/methods: Exponentially growing cell lines/cell stem were irradiated with 1x5 Gy or treated with 1.0μg/ml Ukrain for 2, 6 or 24h. Except colony formation, TP53, p21 and p27 were examined using western blot technique. Analyses of the cell-cycle were performed by flow cytometry.

Results: Ukrain treatment demonstrated a radiosensitizing effect in A549 and U138MG cells and a radioprotective effect in normal fibroblasts. TP53 induction/stabilization (>2-fold) and subsequent induction of p21/p27 (>10-/>8-fold) could be shown in A549 cells and HSF1 after irradiation but not after Ukrain exposure. TP53-overexpression without p21/p27 induction was detected in U138MG cells. An accumulation of cells in the G2-phase after a 24h-Ukrain treatment was detected in A549 (50%) and U138MG cells (70%) whereas the HSF1 showed no alteration of the cell-cycle.

Conclusion: Ukrain did not exert its cytotoxicity via the TP53-pathway. Radioprotection of wt-TP53 cells after Ukrain was TP53/p21/p27-independent and without G1-phase block. However, in tumor cells a radiosensitizing effect was demonstrated that was possibly based on blocking cells in the G2-phase. To provide more insight into Ukrain's unique molecular mechanisms optimal for radiochemotherapeutic approaches further experiments still have to be performed.

748 POSTER

ACE-inhibition with Ramipril improves survival after thoracic irradiation in mice

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Purpose: The doselimiting effect of radiotherapy are in most clinical situations the 'late effects' of normal tissue tolerance. In this study we hypothesize that activation of matrix-metalloproteases may play a part in the pathogenesis of late effects. As Angiotensin Converting Enzyme (ACE) inhibitors have been demonstrated to inhibite at least some matrix-metallo-proteases, it was our hypothesis that they might protect against late irradiation morbidity. In addition we wanted to test if Ramipril had any effect on tumorgrowth.

Methods and materials: Single dose thoracic irradiation to the thorax in C57bl/6J mice was used as a model for late tissue tolerance. We used doses of 12, 15, 18 and 21 Gy and compared mice receiving Ramipril 30 mg/kg, continously 24 hours after irradiation in the drinking water, with mice receiving only plain water. The primary endpoint was survival, and as secondary endpoint for the 12, 15 and 18 Gy experiments we used breathrate measurements every second week for 180 days.

In a second experiment we tested the effect of Ramipril 30mg/kg in a micetumor model using the 'LPB-tumor'.

Results: Mice receiving Ramipril lived significantly longer than controls when the mice were irradiated with 18 or 21 Gy. For the lower doses the difference was not significant, but there was a trend in the same direction. The breathrate measurements supports these results. In Kaplan Meier survival plots with tumorarea $\geq$ 200 mmsq as endpoint we found a significant difference in' survival ' between mice receiving Ramipril and controls for both irradiated and non-irradiated mice.

Conclusions

The ACE-inhibitor Ramipril given 24 hours after single dose lethal thoracic irradiadition significantly prolongs lifetime in C57bl/6J mice. In addition Ramipril attenuates tumorgrowth in LPB tumors in mice.

749 POSTER

Comparison of tumor control probability and normal tissue complication probability between 3D-CRT and IMRT plans in patients with prostate cancer

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Purpose: To compare tumor control probability (TCP) and normal tissue complication probability (NTCP) between conventional three Dimensional Conformal RadioTherapy (3D-CRT) and Intensity Modulated Radiation Therapy (IMRT) in prostate cancer patients using radiobiological response models.

Methods: Ten prostate cancer patients had planning CT studies at the Houston VAMC. The prostate was immobilized using an endorectal balloon inflated with 100 cc of air. The Raptor/3D and Peacock/Corvus treatment planning systems were used to generate 3D-CRT and IMRT