beneficial therapeutic ratio. Such a bioreductive drug will be preferably used in combination with ionizing radiations and/or cytotoxic drugs.

824 ORAL

## HIGH DOSE RATE BRACHYTHERAPY: DOSE ESCALATION IN THREE-DIMENSIONAL MINIORGANS OF THE HUMAN BRONCHUS

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*Aim* of the study was to establish an ex-vivo three-dimensional cell culture system (minorgans) for evaluation of high dose rate brachytherapy in the human bronchus. *Methods:* Non-malignant bronchial tissue was obtained by bronchoscopy. The biopsies were cultured as described (Gamarra F *et al.* Eur. Respir. J. *6* (1993), Suppl. 17, 182s). After 3 weeks the acellular stroma is surrounded by multilayer respiratory epithelium. The miniorgans were then exposed to different dosages of Iridium 192 (30, 45, 60 and 75 Gy). After irradiation the miniorgans were brought back to culture or were incubated in trypsin to obtain a single cell suspension. To measure vitality the cells were incubated for I rain with acridinorange and ethidiumbromid. The percentage of nonvital cells was counted under microscopic view with uv light. *Results:* 10 miniorgans were irradiated. There was no significant difference in vitality between the control group and the group with 30 Gy (10% nonvital cells). The percentage of nonvital cells increased significantly after 45 Gy but remained constant after 60 Gy. The maximum was after 75 Gy (25%). The reincubated miniorgans (45 Gy) were examined after 2 weeks. There were significant more nonvital cells compared to those examined three hours after irradiation (24%). *Conclusion:* Human bronchial epithelium may tolerate higher radiation dosages. Further experiments will focus on time-depending aspects of irradiation induced cell death. This may be of importance for brachytherapy of lung cancer.

825 POSTER

## CELL CYCLE EFFECTS OF TAXOL IN A MURINE TUMOUR AND ITS IMPLICATIONS IN RADIOSENSITIZATION

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The new chemotherapeutic agent taxol (TX) was tested as single agent and combined with an X-ray treatment in a murine mammary carcinoma. Furthermore we performed DNA flow cytometric analysis of tumour cells after *in vivo* TX treatment, to assess the proliferative perturbation of cell cycle. Female hybrid (C3H/RixDBA/2J) mice were used. TX (Paclitaxel, Bristol Myers Squibb P.R.I.) was administered i.p. in single doses of 30, 45, 60, 75 mg/kg b.w.. Irradiation was delivered with an X-ray machine (operating at 15 mA, 250 kV, 0.5 mm Cu filter). TGT4 (the time needed to reach 4 times the initial treatment volume) was evaluated as end-point. In the tested range there was a linear dose-response between tumour growth delay and TX dose. In the combined protocol TX was administered 30 min before a 10 Gy X-ray treatment. Our results in the combined treatments show a linear regression line almost parallel to that resulting in TX alone, with a growth delay of about 6 days. The effect seems to be additive. Flow cytometric analysis demonstrated a G2/M block of tumour cell, induced by both the tested TX concentrations (30 and 45 mg/kg). An increase of G2/M fraction was evident 8 h after treatment, and about 60% of cells were in G2/M within 24 h. After that, cells began again to divide, and after 48 h the percentage of G2/M cells decreased; furthermore, a depletion of cells in S phase was obtained suggesting that TX also avoids the starting of DNA synthesis. Considering these results, combined treatment with an interval of 24 h between TX administration (45 mg/kg) and X-ray treatment (10 Gy) was performed. Although the result obtained with the last schedule was better than the previous one, no significant difference between the two protocols was observed.

826 POSTER

## CISPLATIN, CARBOPLATIN AND IRRADIATION IN HUMAN OVARIAN CANCER CELLS

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Cisplatin (CDDP) and carboplatin (CBDCA) have a similar spectrum of antitumor activity, but a different toxicity. The combination with radiotherapy has been introduced in order to increase therapeutic efficacy. Therefore, we examined whether CDDP and CBDCA interact in the same way with irradiation.,

Human ovarian cancer cells were continuously exposed to CDDP (0.5, 1, 2.5, 5 $\mu$M) or CBDCA (2.5, 5 $\mu$M) 16 h and 4 h before and after irradiation with cobalt 60 $\gamma$-rays. Survival was determined with the clonogenic assay. Interaction was evaluated by determining the dose-enhancement-factors (DEF) and by constructing the isobolograms at different survival levels.

The combination of CDDP and irradiation resulted in an independent cell kill. There was no modification of the survival curve. The DEF = 0.89–1.08 and in the isoeffect-plot the interaction was additive.

Five $\mu$M CBDCA before or 4 h after irradiation resulted in supra-additivity. There was an abolition of the shoulder of the dose survival curve. The DEF >1 (1.69–2.68 at 10% survival) and higher at higher survival levels. In the isoeffect-plot the interactions were supra-additive. The combination with CBDCA 16 h after irradiation (DEF = 0.85–0.96) or at 2.5 $\mu$M (DEF = 1) was additive.

CBDCA induced enhancement of cell kill for irradiation in certain sequences and from a certain dose on. The combination with CDDP was purely additive. In our study, CBDCA was much better than CDDP as far as interaction with irradiation was concerned.

827 POSTER

## RADIOTHERAPY-ENHANCING EFFECT OF IFOSFAMIDE IN HUMAN NSC LUNG CANCER XENOGRAFTS

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The "radiosensitizing" effect of ifosfamide (IFO) was investigated in 6 different human NSCL and 1SCL cancer xenograft, growing subcutaneously in nude mice. Given alone and combined with IFO radiotherapy (RT) was administered in daily fractions of 2 Gy for 10 days. IFO alone was administered at 130 mg/kg/day intraperitoneally on day 0–2. In combined treatments IFO was injected at 100 mg/kg/day 2 hours before RT. Irradiation in combined treatments was given for 7 and 10 days, respectively. Therapy started with average tumor volumes of 200 to 500 $m^3$. IFO increased the effect of RT in 4 out of 7 xenografts. An increase in tumor inhibition and also an additional growth delay was observed in 3 squamous cell carcinomas (LXFE 397, 409, 937) and 1SCLC (LXFS 650). In 1 squamous cell carcinoma (LXFE 839) and the adenocarcinoma LXFA 629 there was no synergistic effect. In the large cell model LXFL 529 IFO alone induced complete tumor remission. Our study demonstrates radiopotentiating effect of IFO in NSCLC and also in the SCLC model, suggesting clinical studies.

828 POSTER

## EFFECT OF EPIDERMAL GROWTH FACTOR (EGF) ON ACUTE RADIATION DAMAGE TO MOUSE INTESTINE AND EPIDERMIS *IN VIVO*

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Epidermal growth factor (EGF) has been shown to play an important role in growth and maintenance of intestinal mucosa and epidermis. The aim of the present study was to investigate if extent and time course of acute radiation damage to epidermis and intestine could be moderated by EGF. Twelve-to-sixteen weeks old female CDF1 mice were treated either by single dose total body irradiation (TBI) or local irradiation to the right hind leg. EGF was given s.c. at a dose of 5 $\mu$g/day for 4 weeks alter radiation. Control animals were treated with isotonic NaCl. During the first week after local radiation weight increased by 10% and 0% in EGF and NaCl treated animals, respectively. However, median skin score was marginal but not significantly smaller in EGF treated animals. Lethality by day 7 alter TBI has previously been shown to be caused by intestinal damage. EGF did not influence day 7 lethality after TBI.