reduce radiation change in BBB and tried to determine the time of maximal stabilization.

Methods: DDO/Lee mice was sacrificed on the 1, 3, 5, 7 and 9 days after whole brain irradiation (single dose 20 Gy) with or without administration of prednisolone and intraperitoneal injection of tryphan blue for gross observation. The radiation change was evaluated microscopically by scoring of histologic damage.

Results: The proportion of vitial staining for radiation-prednisolone group (14/25, 56%). was significantly lower than that for radiation alone group (21/25, 84%). Radiation-prednisiolone group had significantly lower histiologic damage scores for intracellular & interstitial edema ($p = 0.0008$), change of astrocyte ($p = 0.016$) and extravasation of RBC ($p = 0.039$) compared to that of radiation group, respectively. The most prominent differences were noted on 3 days after radiation. The highest histologic damage score was noted on 7 days after radiation. The histologic damage score of radiation-prednisolone group was significantly lower than that of radiation alone group on 3 days ($p = 0.001$) and 5 days ($p = 0.026$) after radiation.

Conclusion: The peak time of acute radiation damage was 7 days after whole brain irradiaton and the prednisolone has significant salutary effect on radiation-induced change of the BBB at 3 and 5 days after whole brain irradiation. Additional experiment with variable dose-fractionation scheme using quantitative mesurement of the change and electromicroscopic examination are necessary.

1340 POSTER

Can GM-CSF reduce oral mucositis? In vitro studies of GM-CSF effects on cultured human and rat oral mucosa epithelial cells

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Purpose: The use of GM-CSF mouthwash has been claimed to be able to reduce the incidence and severity of oral mucositis caused by radiotherapy (Nicolatou-Galitis et al, data presented at the ESTRO-MITRE meeting Brussels, December 2000). Furthermore studies show that locally applied GM-CSF onto the skin leads to keratinocyte growth, which might support the theory that GM-CSF has a direct stimulatory effect on the growth or regeneration of the oral mucosa (Braunstein et al 1994 and Kaplan et al 1993). The aim of the present study therefore was to assess the effect of GM-CSF on the growth of human and rat oral mucosa epithelial cells cultured in vitro.

Method: Human keratinocytes derived from explants of buccal mucosa were cultured as described in details by Arenholt-Bindslev et al (J Invest Dermatol 1987, 88:314-19). Keratinocytes from primary explant cultures were passages to Micro-Well plates (20.000 cells pr well). From 24 hours after seeding, the cells were exposed to graded dilutions of GM-CSF (final concentration in the growth medium, range 10-11-10-5g/ml; 6 wells per conc.; duplicate experiments). At day 3 of exposure, the MTT-assay was performed according to Langkjer et al (J Exp Clin Cancer Res 1993; 12:225-32). Rat oral mucosa epithelial cells (established in culture according to Arenholt-Bindslev et al (see above) were continuously exposed to GM-CSF (4ug/ml) in the medium during 10 days. Cell proliferation was assessed by trypsinization and cell counting on day 3, 7 and 10. Morphology was evaluated by phase contrast microscopy.

Results: No significant cytomorphological, stimulatory or inhibitory effect of GM-CSF was observed in human and rat oral epithelial cells under the experimental conditions.

Conclusion: Based on the present results we suggest that the previously claimed effect of GM-CSF on mucositis may be due to activation of the local humoral defence in the oral cavity (see i.e. Graham et al 1992) rather than to increased proliferation of oral epithelial cells.

1341 POSTER

Cisplatin-induced apoptosis of mesothelioma cells is affected by potassium ion flux modulator amphotericin b and bumetanide

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Purpose: Chemotherapeutic anti-cancer drugs induce cell death by the process of apoptosis. Efflux of potassium ions (K+) is necessary for cell volume reduction during apoptosis and increased inward pumping of K+ thus counteracts apoptosis. Potassium flux modulation could therefore interact with apoptosis and affect the efficiency of cancer chemotherapeutics. We explored if the K+ efflux stimulator amphotericin B, with or without the Na+, K+, 2Cl- -cotransport (K+ influx) blocker bumetanide, could affect cisplatin- and carboplatin-induced apoptosis and cytotoxicity in the pulmonary mesothelioma cell line (P31).

Methods: Apoptosis was determined by quantifying free nucleosomes and caspase-3 activity, and cytotoxicity was determined by clone formation and a fluorometric assay. The pan-caspase enzyme inhibitor Boc-D-FMK was used to further determine the role of caspase activity in K+-flux-modulated cisplatin-/carboplatin-induced apoptosis and cytotoxicity.

Results: Amphotericin B (3.2 mmol/L) combined with bumetanide (100 mmol/L) potentiated cisplatin-induced free nucleosome and caspase-3 activity. The combination of the K+ modulators did, however, not increase cisplatin cytotoxicity. The caspase inhibitor Boc-D-FMK, but unexpectedly also bumetanide, markedly reduced cisplatin cytotoxicity and annihilated the augmented cytotoxicity of cisplatin in presence of amphotericin B. Carboplatin cytotoxicity was reduced by bumetanide, but not affected by amphotericin B. Carboplatin and carboplatin/bumetanide cytotoxicity was further reduced by Boc-D-FMK.

Conclusion: Cisplatin, and to a lesser extent carboplatin, ability to induce apoptosis is indeed influenced by cellular potassium flux modulators. We suggest that K+ ionophores such as amphotericin B, and K+ influx blockers such as bumetanide, alone or in combination, should be further evaluated for their potential clinical usefulness in influencing tumour cell apoptosis induced by cisplatin and other cancer chemotherapeutics.

1342 POSTER

Skin protection by use of sucralfate cream during external beam radiotherapy for breast cancer: a prospective double blind randomized phase II study

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Introduction: Our aim was to investigate if topic aplication of sucralfate cream can reduce the incidence of dermitis, and its overall time to heal when dermitis appears, in patients treated with radiotherapy for breast cancer. Sucralfate is an anti-ulcer drug that has been used to prevent acute radic enteritis during abdominal and pelvic irradiation. Its mode of action is not well known.

Method and Material: 102 patients were included in the study, and 100 were evaluated. A two steps optimal Simon design (phase II) was performed to detect differences of 20% or more between the cream with or without sucralfate, using alpha=0.05, beta=0.2. They were all diagnosed of breast cancer, treated with conservative or radical surgery, and they could receive hormonal therapy or chemotherapy without antracyclines. They had to receive radiotherapy on their breast or toracic wall as part of their treatment, with electrons or 1.2 or 6 MV photons, up to a total dose of 50 to 70 Gy. All of them applied topically on their breast skin a cream, half of them a cream with sucralfate, and the rest the same cream without sucralfate, since the first day of radiotherapy, twice a day, until 2 weeks after the end of radiotherapy or until dermitis solved. The study was double blind, randomized, so that neither patients nor physicians knew the composition of the cream. Validation of the efficacy of the cream was made by the physician following the criteria for cutaneous toxicity of the EORTC-RTOG score and also by the patient following a scale graded 0 to 4 for pruritus.

Results: All patients completed RT. Toxicities for both groups were maximum in the fifth week of treatment, and differences were not statistically significant. In the non-sucralfate group more grade III dermitis were reported (21.6 versus 7.8% in overall treatment, and 11.8 vs 2% at the fifth week).

Conclusion: Sucraltate applied topically does not reduce significatively the indidence of dermitis during breast irradiation, although a slight better tolerance is observed.

1343 POSTER

Scalp cooling in the prevention of anthracycline-induced alopecia

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Introduction: Management of chemotherapy-induced side-effects has improved over the years by better supportive care. Alopecia is therefore increasingly important as a major negative factor in the acceptance of cytotoxic therapy, especially by women. Alopecia is inevitable in anthracycline-based adjuvant chemotherapy for early breast cancer. It is supposed that scalp cooling alleviates hair loss during chemotherapy, but its efficacy is not well proven. A single institution experience with the PinguinR scalp

cooling system is reported. Methods: Between january 1998 and september 2000, 29 patients with early breast cancer received adjuvant or neo-adjuvant CEF (cyclophosphamide 600 mg/m2 d1; epirubicine 60 mg/m2 d1+8; 5-fluorouracil 600 mg/m2 d1) with a scalp cooling system PinguinR. This system consists of four ice-caps consecutively and manually positioned on the scalp, from 25 minutes before until 90 minutes after perfusion of the chemotherapy. Retrospective analysis on chemotherapy-dose and efficacy of scalp cooling, as well as questionnaires on patient acceptance of scalp cooling were assessed. Results: All patients received at least 80% of the planned dose, the majority receiving the full program (24 patients). Fifteen patients (51%) developed alopecia in spite of scalp cooling. One patient terminated the scalp cooling prematurely because of psychological distress, making the success rate of scalp cooling 50%. Side-effects of scalp cooling were pain, headache, dizziness, nausea and vomiting, all reported being a major distress in two thirds of the patients. Nevertheless, 70% of the patients were in favor of the scalp cooling, despite these side-effects. Conclusions: Scalp cooling during anthracycline-based adjuvant chemotherapy for early breast cancer is effective in half the patients. Side-effects of scalp cooling are important but the general appraisal of the treatment is positive.

1344 POSTER

The effect of melatonin on peripheral blood cells during whole body irradiation in rats

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Melatonin, has been reported to participate in the regulation of a number of important physiological and pathological processes. It has also the ability to protect the genetic material of hematopoietic cells of mice from damaging effects of acute whole body irradiation.

Purpose: The objective of this study was to investigate the potential radioprotective effects of melatonin on peripheral blood cells of rats which are whole-body irradiated.

Materials and Methods: Thirteen adult rats were divided into three equal groups, of 10 each. First group was control group received no melatonin or irradiation, second group received total body irradiation (RT) by 5 Gy of gamma-irradiation only, and third group received RT plus melatonin. Five mg/kg of melatonin were given by intraperitoneally, 30 minutes before RT. Second and third groups were sacrificed 1,5 hours following RT. Leukocytes and thrombocytes numbers and hemoglobin levels were measured in all groups.

Results: Table shows the effect of melatonin on leukocyte and thrombocyte counts and Hb levels in all groups. Melatonin significantly increased the number of leukocytes and as well as thrombocytes after gamma irradiation. Additionally, melatonin caused increase in Hb level, but it was no statistically significant compared to other two groups.

Groups	Control	Irradiation	Melatonin plus Irradiation
Leukocyte	5383±337	4387±328*	6116±630*
Thrombocyte	1279167±51293	954000±74984*	1176333±39652*
Hemoglobin	16.65±0.46	16.35±0.68	16.75±0.53

Significant differences (*$p<0.001$) between control and irradiated group and irradiated and melatonin plus irradiated group were statistically analysed by the Student's t-test.

Conclusion: These results indicated that 5 mg/kg dose of melatonin is effective in protection from radiation-induced suppression of peripheral blood cells especially in leukocytes and thrombocytes. Radioprotective effect of melatonin may be via its scavenging for free radicals generated by ionizing radiation and probably stimulating granulacyte-macrophage colony-stimulating factor (GM-CSF) abilities.

1345 POSTER

Toxicity in obese cancer patients treated with chemotherapy calculated according to actual body weight: a prospective study

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Purpose: To prospectively evaluate the incidence of severe toxicity in obese patients (pts) receiving chemotherapy calculated according to actual body weight.

Patients and methods: Among 540 pts with various types of solid tumors treated with different drug regimens, given at conventional doses, 139 (26%) were defined as obese (i.e. body mass index equal or higher than 27.3 kg/m2 in females and 27.8 kg/m2 in males). One hundred and nine of them (20%) received a full dose of chemotherapy during the first cycle and comprised the study group. There were 30 males (28%) and 79 females (72%) with a median age of 56 years (range: 27-85 years). Serious toxicity was defined as neutropenic fever and/or any grade 3-4 non-hematological toxicity (NCI Common Toxicity Criteria). Severe chemotherapy- related toxicity (SCRT) was recorded for the initial three cycles. The criteria for dose reduction and for GCSF administration in subsequent cycles were not modified due to obesity.

Results: The first cycle of chemotherapy was associated with SCRT in 12 pts (11%) (neutropenic fever in 9, grade 3-4 mucositis in 3 and grade 3-4 diarrhea in 2). The second cycle (108 pts) induced SCRT in 5 pts (5%) (neutropenic fever in 5 pts and grade 3-4 mucositis in 2). Two of the 106 (2%) pts who received the third cycle developed neutropenic fever. Due to toxicity, drug doses were reduced during the second, third and fourth cycles in 1, 10 and 3 pts, respectively. There were no treatment-related deaths.

Conclusions: Since the rate of severe toxicity observed in the current study was acceptable, calculation of standard chemotherapy dose according to actual body weight in obese cancer patients seems justified.

1346 POSTER

AEOL 10150, a catalytic antioxidant, reduces the incidence and duration of radiation-induced oral mucositis in a hamster

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Purpose: Mucositis limits the success of cancer therapies and is of complex etiology. Reactive oxygen species appear to play an important mechanistic role in the initiation of a number of the pathways leading to cell damage or death. We hypothesized that AEOL 10150 (AEOL), a catalytic antioxidant that inactivates oxygen-derived free radicals, would reduce the severity of radiation-induced mucositis in a hamster model.

Methods: Hamsters (n=8 per group) left cheek pouches were everted, isolated, and exposed to a single dose of 40 Gy. Two experiments were performed in which animals received AEOL (0.2 ml) either intraperitoneally (IP) or topically (TP) beginning the day (d) before (d -1) radiation (RT), and continuing for 20 d after RT. TP AEOL was applied tid into the RT-treated cheek pouch at doses of 0.25, 1.0, 1.5 and 5.0 mg/ml. IP doses were 0.25, 1.0 and 1.5 mg/ml tid. On alternate days, the cheek pouch mucosa was photographed and at the end of the study, the photographs were graded in blinded fashion on a 6-point scale. Primary outcome a priori was % of days scored >3 (ulceration) by chi-square. Tissues from separate control and 1.5 mg/ml TP and IP treated hamsters (n=3 per group) used for metabolic studies were obtained on d 5 by resecting both cheek pouches at the base.

Results: AEOL IP at all doses, and TP at 5 mg/ml significantly reduced the % days scored >3 ($p<0.05$). IP administration resulted in a 36-59% reduction. Reduction with TP was 36%. AEOL protected ($p<0.01$) against mitochontrial aconitase (AC) inactivation (4-fold -TP, 2.5-fold IP) and 8-hydroxydeoxyguanisine (HDG) formation (1.5-fold, TP and IP), indices of oxidative free radical damage. AEOL concentration was higher in RT than contralateral cheek tissue (2-fold IP, 8-fold TP). AEOL concentration, AC and HDG protection measured at d 5 post RT did not correlate with effect.

Conclusion: Treatment with the catalytic antioxidant AEOL reduces ulceration associated with radiation-induced mucositis. AEOL may act by inactivating oxygen-derived free radicals that initiate processes leading to mucositis and ulcer formation.

1347 POSTER

Tropisetron in the prevention of radiation-induced nausea and vomiting

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Purpose: A prospective multicentre randomized study was designed to