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

investigate the effect of tropisetron for the prevention of nausea and vomiting induced by upper or whole abdominal irradiation.

Materials and Methods: From December 1997 to April 1999, 74 patients were enrolled in a randomized study comparing the antiemetic effect of tropisetron vs. metoclopramide during the upper or whole abdominal irradiation. Sixty-six patients were evaulable. Patients diagnosed with gynecologic, gastrointestinal, urologic malignant tumors or lymphomas and treated with irradiation only were included in the study. All patients were treated with either whole abdominal irradiation (120-150 cGy/daily) or upper abdominal irradiation (150-180 cGy/daily) according to the location of primary tumor. Patients were randomized to the Tropisetron 5 mg. once daily (35 cases) or Metoclopramide 10 mg. t.i.d. (31 cases) for antiemetic therapy on seven days per week throughout the whole radiation treatment (15-42 days). The main efficacy parameter was the occurrence, the number and the severity of nausea and vomiting. Total control was defined as no vomiting or no nausea during the radiotherapy.

Results: Total control of acute emesis was obtained in 79% and 87% of patients receiving tropisetron compared to 50% and 62% of patients receiving metoclopramide in the first and second weeks of irradiation respectively (p=0.037 and p=0.026). However, there was no difference in control of nausea between two groups. At the end of study, the efficacy of the drugs was 'very good' or 'good' for 86% of tropisetron group and 59% of metoclopramide group (p=0.019). All patients receiving tropisetron were judged according to their tolerability as 'very good' or 'good', whereas this rate was 74% for metoclopramide group (p=0.014).

Conclusion: Oral tropisetron given once daily throughout whole radiation treatment is more effective and well tolerable than metoclopramide in the prevention of radiation-induced emesis.

1348 POSTER

Randomised trial with or without amifostin to reduce neurotoxic side effects under chemotherapy with oxaliplatin (L-OHP), FA/-FU (Folfox 3)

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Aim of the study: The chemotherapy with L-OHP, FA, 5-FU has a high activity by advanced colorectal cancer (ACRC). The main dose limiting toxicity of a chemotherapy with L-OHP is an peripheral sensory neuropathy. In this study become the patients (pts.) a chemotherapy with L-OHP, FA and 5-FU with or without amifostin. The question was the reduction of side effects of neurotoxicity after application of amifostin.

Materials and Methods: We've included 34 pts. with a ACRC. The median age was 60 years. Karnofsky status was 90%. In Arm A chemotherapy was applicated with L-OHP 85mg/m2 d1, FA 500mg/m2 d1+d2 and 5-FU 4000mg/m2 over 48h continuos infusion as beweekly schedule. In arm B was 910mg/m2 Amifostin over 10 min i.v. before application of the same schedule of chemotherapy. Investigation of toxicity, neurological examination and a blood count was performed in front of every cycle. For a daily documentation of the side effects every pts. became a questionary.

Results: The Amifostin-group showed a significant reduction of peripheral neurotoxicity (p=0,048). In the amifostin group occur leucopenia II/III° in 1,3% of all cycles and in the controlgroup in 9,8%. Thrombopenia was observed in the controlgroup in 4 pts. and in null in pts. in the Amifostin-group. Side effects like nausea, mucositis and diarrhoe showed not differences. The tumorresponse is not comperable, because of different the distribution of first-, second- and third-line therapy in both groups.

Conclusion: It seems that side effects under chemotherapy including L-OHP, FA/5-FU could be reduced under supportive care with amifostin.

1349 POSTER

An NK1 antagonist versus a 5-HT3 antagonist in patients receiving high dose cisplatin: comparison of the time course of acute emesis provides a rationale for combination therapy

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Background: The efficacy of neurokinin 1 receptor antagonists (NK1 RAs) in reducing acute and delayed cisplatin-induced emesis has been demonstrated. Their particularly robust effects in delayed emesis may differentiate this new class of antiemetic from 5-HT3 receptor antagonists (5-HT3 RAs), the activity of which is less notable in the delayed phase. Combinations with existing antiemetics are likely to maximize the efficacy of NK1 RAs. To develop a rationale for such combination therapy, we examined the time course of acute emesis after L-758,298(L), prodrug for the selective NK1 RA, MK-0869, and that after the 5-HT3 RA ondansetron (OND) in patients receiving high dose (>50 mg/m2) cisplatin. Historical rates of acute emesis after this dose of cisplatin are virtually 100% in patients receiving no prophylaxis, with a median time to first emesis of <2 hours. Efficacy results of this study have been previously reported (Eur J Cancer 37:835-842,2001).

Methods: Double-blind, randomized, active-agent controlled study. 30 pts received L 60 or 100 mg iv & 23 pts received OND 32 mg iv.

Results: In the Overall acute phase (0-24h), no-emesis rates were 37% with L and 52% with OND (p=0.57). The temporal patterns of acute emesis following L compared with OND were notably different. The percentage of patients with acute vomiting at 0-8h, 8-16h, 16-24h, and Overall (0-24h) for the L group were 63%, 0%, 0%, and 63%, respectively, whereas the percentages for the ondansetron group were 17%, 13%, 17%, and 48%. The median time to first emesis was 4.46h in the L group and 12.25h in the OND group, with all acute failures in the L group occurring in the first 8h.

Conclusions: These results support the hypothesis that Substance P is a primary mediator of 'later' acute emesis while 'early' acute emesis may be more heavily influenced by serotonin. If correct, these hypotheses provide a strong basis for combining 5-HT3 RAs and NK1 RAs for the prophylaxis of acute cisplatin-induced emesis. Currently, the combination of an NK1 RA, a 5-HT3 RA, and dexamethasone has been shown to provide the best control of acute emesis among existing therapy options.

1350 POSTER

Using 'In silico mouse' for predicting therapeutic protocols on thrombopoiesis

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Background: Thrombocytopenia is a common hazardous blood condition appearing in different clinical situations, including cancer chemotherapy. A thrombopoiesis-controlling cytokine, thrombopoietin (TPO) shows dramatically increased blood platelet counts, thus improving a patients' ability to withstand chemotherapy.

Aims: To develop an efficient method for predicting the effects of different drug treatments on murine thrombopoiesis and, in particular, for suggesting improved TPO protocols.

Methods: We simulated TPO and cytotoxic drugs effects on murine thrombopoiesis, by translating the driving biological, pharmacological and clinical interactions into an elaborate mathematical and computation system. The result is an 'In silico Murine Bone Marrow tool', which predicts diverse treatment effects on murine thrombopoiesis. The tool was evaluated by its ability to retrieve published data from murine experiments involving TPO administration. After verification the tool can be used for the design of improved therapeutic protocols.

Results: The 'In silico Murine Bone Marrow tool'was quick and efficient in retrieving diverse published results involving different TPO protocols. When presented with previously untested protocols, the tool yields elaborate results that are biologically and medically sound. The different thrombopoiesis lineage cell counts, as well as the TPO concentrations are graphically and numerically presented in various time resolutions, and platelet counts' decrease/increase below/above relevant medical thresholds (e.g. thrombocytopenia, thrombocytosis, transfusion indicating levels etc.), these can be alerted on-line during the simulation. When used to explore optional protocols, the tool yields protocols that are improved in clinical outcome and/or more efficient in their use of TPO.

Conclusions: The 'in silico murine bone marrow tool' can be used to retrieve experimental results and to plan better TPO protocols. In another work we develop an 'in silico human bone marrow tool'which has already been verified retrospectively. Using such 'In Silico' methods at the research level, may accelerate the design of effective treatment protocols, thus reducing the number of experiments, and of patients and laboratory animals that are subject to potential hazards, and hence bring the cost-reducing advantages and time-reduction of clinical trials undertaken by pharmaceutical companies.