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D-lysine for reduction of renal [In-111-DTPA,D-Phe-1]-octreotide and [Y-90-DOTA,D-Phe-1,Tyr-3]octreotide uptake

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In-111-DTPA-octreotide (In-111-DTPAOC), successfully used to image somatostatin receptor-positive lesions, is now applied for peptide-receptor-radionuclide therapy (PRRT). For the latter purpose [DOTA,D-Phe-1,Tyr-3]octreotide (DOTATOC), suitable for stable radiolabelling with Y-90, is even more promising. However, significant renal (re-)uptake and retention of these analogues exists, reducing the detection sensitivity of perirenal tumours and increasing radiotoxicity in the kidney during PRRT. We studied the inhibitory effects of D- and L-lysine on kidney uptake of In-111-DTPAOC and Y-90-DOTATOC.

Methods: Wistar rats were given In-111-DTPAOC (0.2 MBq, 0.5 μg–0.5 mg; iv, ip or orally) or Y-90-DOTATOC (1 MBq, 0.5 μg; iv), with or without D- or L-lysine. At several time points, organs were isolated and counted.

Results: D- or L-lysine, iv, 400 mg/kg, resulted in >50% inhibition of kidney In-111-DTPAOC uptake. Higher or repeated doses of lysine did not increase inhibition. Oral and ip administration of lysine was less effective. However, after L-lysine also uptake of In-111-DTPAOC in target organs was decreased. D-lysine did not have this negative effect. Renal uptake of Y-90-DOTATOC was reduced by 65% by D-lysine iv; uptake in target organs was unaffected.

Conclusion: D- and L-lysine are promising for reduction of nephroradiotoxic effects during PRRT by preventing tubular re-uptake of the radiolabel. This method may be useful in other nephrotoxic modalities as well. D-lysine is preferred to obtain maximal radioactivity in the tumour.

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Randomised controlled trial of supportive care in radical pelvic radiotherapy: Does it influence radiation morbidity?

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Purpose: This study evaluates the effect of a patient focused approach led by a nurse specialist vs. conventional management. The hypothesis is that supportive care could prevent and minimise the impact of radiation induced side-effects.

Methods: This study is designed as a randomised controlled clinical trial with a sample of 115 men who have undergone radical pelvic radiotherapy (64Gy) for prostate (n = 95) or bladder cancer (n = 20). Data for each patient was collected during radiotherapy and in a 5 month follow up period from entering the study; patients completed EORTC QL30 and self report visual analogue scale of symptoms, satisfaction with care and economic costs.

Results: Initial analysis suggests a reduction in bladder ($p = 0.04$) and bowel morbidity ($p = 0.01$) in the early part of radiotherapy treatment and better emotional functioning at 6 weeks ($p = 0.04$) in the intervention group. This resulted in improvement of global quality of life scores ($p = 0.02$), although some of these advantages are lost by 12 weeks.

Conclusion: These results suggest that that non pharmacological management of symptoms was effective in reducing symptoms and in improving quality of life of patients during radiotherapy. This study identifies the value of nurse specialist care, within a multidisciplinary team, not only economically but also for patients quality of life.

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Post radiation severe xerostomia relieved by pilocarpine: A prospective French cooperative study

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From June 1995 to February 1996, 156 patients (pts) with severe radiation induced xerostomia received Pilocarpine hydrochloride orally, 15 mg per day with a 5 mg optional increase at 5 weeks up to a daily dose of 25 mg beyond 9 weeks. The aim of the study was 1) to confirm the action of the drug against xerostomia, 2) to correlate the response to dose/volume radiotherapy parameters. 145 patients are fully evaluable. Treatment compliance was 75%. 38 pts (26%) stopped treatment before week 12 for acute intolerance (sweating, nausea, vomiting) or no response. No severe complication occurred. 97 pts (67%) reported a significant relief of symptoms of xerostomia at 12 weeks. Within 12 weeks, the size of the subgroup with normal food intake almost doubled (13 to 24 pts) while the size of the subgroup with (nearly) impossible solid food ingestion decreased by 38% (47 vs 29 pts). The impact on quality of life was considered important or very important by 77% of the responders. No difference was found according to dose/volume radiotherapy parameters suggesting that oral Pilocarpine hydrochloride 1) acts primarily by stimulating ectopic salivary glands, 2) can be of benefit to pts suffering of severe xerostomia regardless of radiotherapy dose/volume parameters. 3) All responders are identified at 12 weeks.

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A phase III randomised study of carboplatin and amifostine (A) vs carboplatin and G-CSF in patients with inoperable non small cell lung cancer (NSCLC)

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Purpose: Amifostine is an organic thiophosphate which protects normal tissues from the effects of chemotherapy. This study is designed to compare the haematological toxicity seen when either A or G-CSF is given to patients with advanced NSCLC treated with carboplatin at a dose of AUC 9.

Methods: Patients are randomised to receive carboplatin AUC 9 with either A 740 mg/m^2 pre and 2 hours post carboplatin or G-CSF (263 μg/day) from days 2–15. Treatment is repeated every 28 days. 20 patients are currently evaluable for haematological toxicity, 9 with G-CSF and 11 with A.

Results: Of those patients treated with G-CSF, 4 have developed Grade 3 and 5 have developed Grade 4 thrombocytopenia. The dose of carboplatin has been reduced in 5 patients and 3 patients have required platelet transfusions. In contrast, only 2 patients receiving A have developed grade 3 and no patients have developed grade 4 thrombocytopenia. There has been 1 dose reduction and no platelet transfusions administered. No patients have developed grade 4 neutropenia. The response rate and survival are preliminary at this stage but there is no evidence of reduced antitumour activity with A.

Conclusion: The data suggest that amifostine protects against both neutropenia and thrombocytopenia whereas G-CSF protects against neutropenia alone.

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Amifostine protects against acute cisplatin/ifosfamide-induced kidney damage assessed by measurement of glomerular and tubular enzymes

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Purpose: This study evaluates the degree of kidney damage during cisplatin (P)/ifosfamide (IFO)-combination chemotherapy (CTX) and its possible prevention by amifostine (AMI) using an established model for the quantification of urinary markers.

Patients and Methods: 26 pts with solid tumours stratified according to pretreatment who received VIP- or TIP-regimen containing P (50 mg/m^2, d1 over 1 h) and IFO (4 g/m, d1 over 16 h) were randomized to VIP/TIP+G-CSF alone or with AMI 910 mg/m^2 given as a short infusion prior to CTX. For all pts creatinine-clearance (Cc), serum creatinine and electrolytes including magnesium (Mg) were determined prior to and after each cycle. Differential urinary protein and enzyme excretion was measured at days 0, 3 and 5 after CTX. High molecular weight proteins (HMW) were used to target the glomerular, low molecular weight proteins (LMW) and N-acetyl-D-glucosaminidase (NAG) excretion to detect proximal tubular damage.

Results: 26 pts were evaluable (14 with AMI and 11 controls) for urinary markers and 30 pts for Cc and Mg values. AMI prevented a significant reduction in Cc after application of 2 cycles of P/IFO-based CTX and reduced the excretion of tubular markers (LMW, NAG) by appr. 50% (day 5) as compared to controls ($p < 0.05$). The degree of prevention was more pronounced with every cycle of CTX. Cc was 121 ml/min (65–159) prior to and 126 ml/min (80–162) after CTX in the AMI-group, whereas in the

control-group a decrease from 118 ml/min (66–174) to 88 ml/min (60–157) was observed ($p < 0.05$). The incidence of low Mg serum levels during treatment was 10% with AMI vs. 63% in control pts ($p < 0.05$). Mg levels recovered almost completely in both group at the end of cycles (94% vs. 83% of starting levels).

Conclusion: The use of early urinary markers allows to detect tubular kidney alterations even after the first application of P/IFO. AMI was identified to have protective effects against P/IFO associated nephrotoxicity indicating by significantly reduced urinary excretion of LMW/NAG, constant levels of Cc after 2 therapy cycles and a lower incidence of hypomagnesemia.

57 ORAL

Effectiveness of antiemetic drugs in prevention of chemotherapy (CT)-induced acute emesis

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Purpose: Efficacy obtained by treatment in clinical trials can be different from that achieved in daily practice. No data on this problem, at least for antiemetic treatment of CT-induced emesis, are available. A prospective drug utilization study at 33 Italian oncological centers.

Methods: In June 1996, for two consecutive weeks, all adult patients (pts) starting any CT, were blindly monitored for antiemetic prescription. Excluded from the study were pts with acute leukemia and pts receiving high dose CT or radiotherapy. Response to antiemetic therapy was evaluated by interviewing pts by phone 24 hrs after.

Results: 1220 patients (pts) receiving one-day CT were evaluable. Complete protection from vomiting/nausea was obtained in 75.7%/61.4% of 140 pts receiving cisplatin (CDDP)-based CT, in 81.8%/52.6% of 742 pts receiving moderately emetogenic CT (MEC) (carboplatin, epirubicin, doxorubicin, cyclophosphamide and mitoxantrone) and in 91.7%/71.6% of 338 pts receiving low emetogenic CT (i.e., gemcitabine, vincristine, vinblastine, vinorelbine, etc.). Complete protection from vomiting/nausea in pts receiving CDDP was 79.4%/68.2% if they received the standard combination of corticosteroids plus a 5-HT_3 receptor antagonist and 63.6%/39.4% if not, while in pts receiving MEC it was 84.7%/79.7% and 56.4%/49.8%, respectively.

Conclusion: The rate of protection from emesis achieved in these patients is not different from that obtained in those enrolled in clinical trials despite the fact that a great variety of doses and schedules of the various antiemetics (in particular corticosteroids) was observed.

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Lung cancer after therapy of Hodgkin disease: Influence of treatment and smoking

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Purpose: To retrospectively evaluate the risk of lung cancer after therapy of Hodgkin's disease in a single institution.

Methods: Medical records of 2,391 patients receiving therapy for Hodgkin's disease from 1961 to 1993 (mean follow-up, 10.6 years) were analyzed. Risks for lung cancer incidence were calculated by comparison with expected rates for the general population matched by age and race.

Results: From 1961 to 1993, 41 patients developed lung cancer, yielding a relative risk of 8.96 (95% confidence interval [CI] = 6.2–11 7). Relative risk was 7.2 (95% CI = 4.3–9.0) after radiotherapy alone, 10.7 (95% CI = 5.9–16) following chemoradiotherapy, and 11.0 (95% CI = 4–24.5) after salvage chemotherapy following radiotherapy. No one treated with chemotherapy alone developed lung cancer. Forty of 41 lung cancers (97.6%) arose in the irradiated field. Thirty-eight of the 41 patients (92.7%) had a history of smoking.

Conclusions: Lung cancers arose predominantly in the irradiated field and were strongly associated with smoking. Limiting the lung volume irradiated and avoiding smoking may reduce the subsequent risk of lung cancer.

59 POSTER

Protection of salivary glands by amifostine in patients treated with high dose radioiodine

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Purpose: Salivary gland impairment following high dose radioiodine treatment (HD-RIT) is a well recognized side effect. Since differentiated thyroid cancer (DTC) has a very good prognosis reduction of long-term side effect becomes more important. Therefore, the radioprotective effect of amifostine (Ethyol®) was investigated in patients receiving high dose radioiodine therapy.

Methods: Quantitative salivary gland scintigraphy was performed in 17 patients with DTC prior to and 3 months after radioiodine therapy with 6 GBq I-131. Eight patients were treated with 500 mg per sqm b.s. prior to radioiodine, and 9 patients served as control.

Results: In 9 controls HD-RIT significantly ($p < 0.01$) reduced pertechnetate uptake by 37% and 31% in parotid and submandibular glands, respectively. Three out of these 9 patients exhibited xerostomia grade I. In contrast, in 8 patients treated with amifostine there was no significant ($p = 0.878$) decrease in parenchymal function following HD-RIT, and xerostomia did not occur in any of them.

Conclusion: Parenchymal damage in salivary glands induced by HD-RIT can be reduced significantly by amifostine. This may help to increase quality of life of these patients.

60 POSTER

Effect of 5-fluorouracil (5-FU) infusion in myocardial perfusion scans

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Purpose: The cardiotoxicity of 5-FU is frequent (12.5%) and manifests usually by acute coronary events. The aim of this study was to assess the effect of the drug in the coronary blood flow.

Methods: During a 40 months period, 45 patients (M/F: 39/6, mean age: 59 years) with advanced head and neck cancer and normal cardiac function were included prospectively in a chemotherapeutic protocol with continuous IV infusion of 5-FU 1000 mg/m^2/day for 5 consecutive days. The evaluation of the myocardial perfusion was based on dipyridamole thallium-201 cardiac imaging and included 2 scans for every patient: (1) a dipyridamole thallium-201 heart scan before the initiation of chemotherapy, and (2) after one month, using the same imaging protocol and the same doses of dipyridamole and thallium-201, a heart scan while the patient was under the continuous IV infusion of 5-FU (3rd–4th day). The comparison of the 2 scans and the quantification of the results were based on the computer programme of the University of Alabama.

Results: There was a statistically significant decrease in the myocardial thallium-201 uptake during the IV 5-FU infusion ($p < 0.001$). This decrease was equivalent to 24.5% and was equal in all myocardial segments.

Conclusion: The infusion of high doses of 5-FU results in a great reduction (24.5%) of the myocardial perfusion. This effect could trigger the acute cardiotoxicity events observed mainly in patients with preexisting critical coronary stenoses.

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Intensive radiochemotherapy (RCT) with amifostine (A) in head and neck (H&N) cancer

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Purpose: We evaluated the ability of A to protect against the toxicities induced by intensive RCT for H&N cancer in a 3 arm study.

Methods: 25 patients with H&N cancer received primary or adjuvant radiotherapy (2Gy, 5days/week to 60Gy) and either carboplatin 70 mg/m^2 on days 1–5 and 21–25 (arm A, n = 10) or, carboplatin 70 mg/m^2 on days 1–5 and 21–25 and 5-FU 600 mg/m^2 administered over 16 hours on days 1–5 and 21–25 (arm B, n = 8). Both groups of patients received 500 mg A prior to carboplatin. Patients in arm C (n = 7) received chemotherapy as in arm B plus an additional dose of A (250 mG) prior to each infusion of 5FU.