Conclusions: This study suggests the possibility of an association of the GC genotype in G915C and a protection effect against prostate cancer (Odds Ratio: 0.20; 95CI 0.07-0.57); however, further studies must be carried in order to clarify this association.

813 POSTER

Erythropoietin therapy: Is there a place in advanced prostate cancer-related anemia?

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Background: Cancer-related anemia contribues to comorbidity of disease and may compromise tolerability, efficacy of therapy and impairs quality of life. The etiology of this anemia is multifactorial.

Purpose: To avaluate the impact and the predictive criteria for using rhEPO in patients with Advanced Androgen Independent Prostate Cancer (AAIPC).

Population and Methods: We studied 14 patients with AAIPC and cancer-related anemia (Hb < 80 g/L and transfused-dependent). The anemia was characterized and any correctable cause of anemia have been ruled out. The iron status was evaluated and monitored. Ten patients were treated with rhEPO at a median dose of 100–150 U/kg BW 3 times a week, during a median period of 8 weeks.

Results: Baseline erytropoietic status showed a correlation between serum EPO and Hb in 11 patients - adequate observed/predicted log EPO ratio. Defective erythroid marrow activity evaluated by bone marrow aspirate/biopsy. Three patients demonstrated a median Hb increase of 20 g/L (responders) and two showed a increase of 12 (partial responders). We didn't find anti-erythropoietin antibody levels, and also no major adverse effects.

Conclusions: Our results show that the presence of defective endogenous EPO production is a strong indicator of a good response. Anemia in these patients is mainly due to defective bone marrow even in the presence of an adequate scrum EPO, suggesting others inhibitory cytokines. The best response predictors to rhEPO treatment were EPO levels < 100 U/L and a baseline reticulocyte count > 1.5%.

814 POSTER

Open-label phase II study of ZD0473 in patients with metastatic hormone refractory prostate cancer

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Aims: ZD0473 (cis-amminedichloro[2-methylpyridine]platinum [II]) is a new generation platinum drug designed to have an extended spectrum of antitumour activity and overcome platinum resistance mechanisms. A multicentre, open-label, Phase II study was designed to evaluate the response rate, duration of response, and tolerability of ZD0473 as single-agent therapy for patients (pts) with metastatic hormone resistant prostate cancer.

Methods: Pts received ZD0473 120 mg/m2 as a 1-h iv infusion on day 1, every 3 wks. A CT scan was performed on each pt every 6 wks, and RECIST response evaluation criteria used for assessment until progression. A 2-stage recruitment was planned, with 10 pts to be initially recruited in stage 1 and a further 19 pts in stage 2 (recruitment to stage 2 is dependent on ~ 1 OR being observed in stage 1).

Results: To date, 10 pts (median age 66 years [range 58-76]; WHO performance status 0 or 1) have been recruited onto stage 1 of the trial. All pts had histologically-confirmed adenocarcinoma of the prostate. Hormone resistant disease had been confirmed in all of the pts by serological, radiographical or symptomatic progression. Pts had not received flutamide or bicalutamide within the previous 4 or 6 wks, respectively.

Pts have received a total of 31 cycles of ZD0473 (median number per patient 3 [range 1-5]); only 1 pt received a dose reduction (no pts were dose escalated). 9 pts were evaluable for tolerability. The main dose-limiting adverse events rated as G3/4 were thrombocytopenia (G3 [10 episodes]), anaemia (G3 [3]) and neutropenia (G3 [2]). Nausea and vomiting were well controlled with 5-HT3 antagonists and steroids. There was no evidence of ototoxicity, neurotoxicity or renal toxicity. There was 1 episode of febrile neutropenia and no treatment-related deaths. Of 8 pts evaluated for efficacy, 2 had a PR on radiological criteria and had a prostate-specific antigen (PSA) PR (reduction in PSA >50%). 2 additional pts had a minor reduction of PSA, with SD on radiographic assessment. 3 of the 8 pts were withdrawn due to progression.

Conclusion: The manageable tolerability profile of ZD0473 and an OR in 2/8 pts with hormone resistant metastatic prostate cancer justifies the continuation of this Phase II study.

Renal and bladder cancer

815 POSTER

Prognostic value of circulating extracellular DNA in bladder cancer patients

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Introduction: Circulating extracellular DNA has been detected in the serum of various types of tumors, including early stage, suggesting that serum DNA could be a marker of circulating micrometastases. The objective of our study was to isolate DNA from the serum of bladder cancer patients obtained at different times during follow-up and to correlate its presence with the stage of disease and the risk of death.

Patients and methods: A 10 ml blood sample was collected from 68 patients (pts) with bladder tumors. DNA analysis was carried out in 25 pts with metastatic or relapsed tumors, 17 pts with locally advanced tumors and 26 pts with no evidence of disease after cystectomy. DNA was extracted from plasma and blood lymphocytes using QI Amp blood kit (Qiagen). Cut-off DNA level, based on the analysis of healthy controls, was established at less than 4.5 ug/ml.

Results: Forty one (60%) pts had a DNA value over 4.5 ug/ml. Seventeen (68%) pts with metastatic tumors, 10 (58%) pts with locally advanced tumors and 14 (53%) pts disease-free after cystectomy had a high DNA concentration (> 4.5 ug/ml). The mean DNA concentrations i the three groups of patients were 7.0 ug/ml (range 2 to 17), 5.8 ug/ml (range 2 to 18) and 5.1 ug/ml (range 1 to 11), respectively. DNA concentration after cystectomy correlated with prognosis; 7 of 17 (41%) pts with high DNA level died, whereas only 1 of 15 (6%) pts with a DNA concentration below 4.5 ug/ml died due to tumor progression (Fisher exact test, p=0.04).

Conclusions: Concentration of circulating extracellular DNA correlates with state of disease. Furthermore, a high level of DNA after cystectomy confers a poor prognosis and could help in selecting patients with high risk of relapse who could be candidates for adjuvant chemotherapy.

816 POSTER

Acute and late morbidity in patients with bladder carcinoma treated with ARCON (Accelerated Radiotherapy, Carbogen and Nicotinamide)

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Background: A phase II trial of ARCON was undertaken in patients with muscle-invasive bladder carcinoma to evaluate carbogen and nicotinamide as modifiers of chronic and acute hypoxia respectively in this setting.

Method: All received accelerated, radical radiotherapy with 55Gy in 20 daily fractions over 4 weeks. Between January 1994 and July 2000, a total of 107 patients with minimum follow-up of 6 months have been included: 10 received nicotinamide alone during radiotherapy, 53 carbogen alone and 44 received carbogen and nicotinamide. Weekly morbidity scores were collected for the first 10 weeks followed by 6 monthly assessments.

Results: Acute reactions peaked at week 6 for urinary endpoints (frequency, nocturia, dysuria, urgency, hæmaturia, incontinence). The increase in frequency was severe in 35±11% (± 1SD) of patients; nocturnal frequency = 7 was present in 17%; 10±7% reported incontinence, of whom half required a urethral catheter. Intermittent clinical hæmaturia was observed in 5%. Bowel morbidity peaked at 3±4 weeks when one fifth of patients recorded liquid stools and a fæcal frequency of =10. Severe bleeding was seen in 3%; a similar proportion experienced severe suprapubic pain. All acute reactions returned to baseline levels by week 10. Between 12±24 months moderate/severe late urinary frequency developed in 15% and nocturia = 4 times was seen in 5%. No other bladder or bowel severe morbidity in the absence of tumour recurrence was observed during this interval. There was no significant difference in severity or duration of early or late reactions, between carbogen alone and carbogen with nicotinamide. The 12 month cystoscopic local tumour control rate was 81% and overall

survival was 76%. A Phase III multicentre randomized trial is currently ongoing in the UK funded by the Cancer Resaerch Campaign.

817 POSTER

Serum IGF-I, leptin and body mass index in relation to survival in patients with renal cell carcinoma

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Purpose: Obesity is associated with an increased risk of certain cancers, including renal cell carcinoma. Possible mediators of this increased risk are insulin-like growth factor-I (IGF-I) and leptin. Whether these hormones affect prognosis has not been studied.

Methods: We analysed serum leptin at the time of diagnosis in 205 consecutive patients with renal cell carcinoma. Serum IGF-I and body mass index (BMI) was assessed in 197 of these patients. Serum IGF-I decreased with age, but did not correlate to gender, BMI, tumour stage or grade.

Results: Leptin was significantly higher in female compared with male patients, and correlated to BMI. Serum leptin was unrelated to tumour stage, but inversely related to nuclear grade, parallelled with a decrease in BMI. Survival analysed in relation to serum IGF-I showed that patients with levels above median had a more favourable prognosis, compared to those with lower levels ($p = 0.06$). For serum leptin patients with levels in the lowest quartile tended to have a shorter survival time compared to those with higher levels. A multivariate analysis showed that tumour stage, nuclear grade and serum IGF-I were independent prognostic factors for survival.

Conclusions: High serum levels of IGF-I were associated with a more favourable prognosis in patients with renal cell carcinoma. However, serum leptin levels and BMI did not affect prognosis.

818 POSTER

Lymphatic mapping and detection of sentinel node in patients with urinary bladder cancer

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Objective: To determine whether it was possible to detect sentinel nodes in patients with bladder cancer, and to investigate if the histopathological status of identified sentinel nodes reflected the status of the routinely excised lymphatic field

Materials and methods: 13 patients with bladder cancer who met criteria qualifying for radical cystectomy, were examined preoperatively with injection of radioactive tracer peritumorally, then followed by lymphoscintigraphy and during operation (surgery) with dye marker and Geiger-meter to visualise lymphatic drainage and detect sentinel nodes. Identified sentinel nodes were compared histopathologically with other routinely excised lymph nodes

Results: Sentinel nodes were detected in 85% of the cases. In four patients histopathology confirmed lymph node metastasis, in each case metastasis was confined to the detected sentinel node. In one case only was the lymph node metastasis an obturator node

Conclusions: Sentinel nodes can be detected in patients with urinary bladder cancer using these methods, regional lymph node metastases, if present, were located in correponding sentinel nodes and the principles of lymph node dissection solely in fossa obturatoria need to be further scrutinized

Testicular cancer

819 POSTER

Environmental or hereditary risk of cancer in testicular tumor patients?

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Purpose: The common environment of the relatives, i.e. of brothers and offspring, and the doubled worldwide incidence of testicular cancer over the past 25 years suggest the strong involvement of the environmental factors in the formation of testicular cancer. Familial cancer-aggregations and the occurrence of bilateral tumors in the patients seem to be arguments in favor of the major influence of genetic factors. The aim of this study was to sort out the role of hereditary components in testicular tumor patients (TTPs) by determining cancer occurrences in their families, *versus* occupation- and fertility-rate matched normal controls.

Methods: Familial aggregation of testicular- and other cancers were investigated in first degree relatives of 293 TTPs and 600 age matched controls, under the same socioeconomic and environmental circumstances.

Results: The incidence of cancers was significantly higher in TTP families than in the controls (10% vs. 7.9%), but this result could be accounted for almost entirely by the finding of more cancers in brothers (11.2% vs. 3%) and offspring (3% vs. 0% in controls, and/or 15.3/100 000 prevalence of childhood tumors in Hungary). There was no association with other cancers except testicular malignancy in 5 brother-brother pairs and one father-son case. Two percent of patients reported familial, and 1.7% had bilateral testicular cancers. Significant shift was found in the sex-ratio of the descendants: Testicular cancer patients fathered more girls than boys (58%:42% vs. 47%:53% in controls). Six cancers occurred in 200 offspring of 153 TTP families (bilateral Wilms' tumor, neuroblastoma, brain tumor, acute lymphoid leukemia, testicular tumor and histiocytosis-X), while no cancer was found in 423 offspring of 600 normal controls. As a form of genetic instability increased yield of spontaneous chromosomal aberration was detected in both index patients and their offspring (2% and 0.90% vs. 0.87% and 0.62% in controls).

Conclusion: The familial aggregation of testicular malignancy in brothers, the altered sex ratio in the offspring, the dramatically increased incidence of childhood tumors, and the elevated frequency of chromosomal aberrations in index patients and their offspring under the same socioeconomic conditions indicate more significant role of hereditary factors in the predisposition to testicular- malignancy than that of environmental factors.

820 POSTER

A phase II study of alternating dose-dense chemotherapy in patients with poor-prognosis disseminated non-seminomatous germ cell tumors (NSGCT): Final results

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Purpose: To assess the efficacy and toxicity of a dose-dense chemotherapy regimen in patients with poor-prognosis NSGCT.

Patients and Methods: Poor-prognosis NSGCT was defined as follows: at least two sites of non pulmonary metastases, an extragonadal primary tumor, HCG > 10,000 mIU/mL, or AFP > 2,000 mIU/mL. Cycles of the BOP-CISCA-POMB-ACE regimen (bleomycin, vincristine, cisplatin/cisplatin, cyclophosphamide, doxorubicin/cisplatin, vincristine, methotrexate, bleomycin/etoposide, dactinomycin, cyclophosphamide) + G-CSF were recycled every 7 to 14 days.

Results: 58 patients were enrolled: 38 (66%) poor-prognosis and 19 (33%) intermediate-prognosis according to the IGCCCG. Median number of courses: 2.5 (range 0.25–5). 42 patients (72.4%) had a complete response. With a median follow-up of 31 months (range 0.3 to 71 months), the 3-year overall survival (OS) rate was 73% (95% CI: 62%–86%). The 3-year OS rates were 83% (95% CI: 67%–100%) in the intermediate-prognosis group and 67% (95% CI: 53%–84%) in the poor-prognosis group. Toxicity: G4 neutropenia (79%), G4 thrombocytopenia (69%), G4 anemia (22%), G4 stomatitis (19%), and 4 early deaths (7%).

Conclusion: The dose-dense BOP-CISCA-POMB-ACE regimen is highly active in patients with NSGCT with intermediate- or poor-prognosis according to the IGCCCG. Because outcomes with this regimen compare favorably with outcome after standard therapy, dose-dense chemotherapy should be further investigated in this subset of patients.