Conclusions: the combination of G plus P demonstrated to be very active and tolerable in TCC ushering us in *the post-M-VAC era* for TCC pts.

1406 POSTER

Combination chemotherapy with cis-platin (CDDP), epirubicin (EPI), and docetaxel (DOC) in transitional cell urothelial cancer (TCC). A phase II study

D. Pectasides, A. Visvikis, A. Aspropotamitis, A. Halikia, A. Kalantaridou, S. Batzios, N. Karvounis, A. Athanassiou. *1st Dept. of Medical Oncology, Metaxa's Memorial Cancer Hospital, Piraeus, Greece*

Purpose: This study was conducted to evaluate the efficacy and toxicity of the combination of CDDP, EPI and DOC in locally advanced or metastatic urothelial TCC.

Methods: Thirty-two chemotherapy (CT) – naïve patients (pts) were treated with EPI 40 mg/m^2 I.V., DOC 75 mg/m^2 I.V. with standard oral steroids premedication and CDDP 75 mg/m^2 I.V. with pre and post-hydration. Treatment was repeated every 3 weeks. Pts were evaluated for toxicity weekly and assessed for response every 2 cycles of CT. Twenty-four pts had metastatic and 8 pts locally advanced disease. There were 6 female and 26 male with a median age of 65 y. The ECOG PS was 0 in 10 pts, 1 in 6, 2 in 2 and 3 in 4.

Results: There were 9 (30%) CRs (2, 28.5% in locally advanced and 7, 30.4% in metastatic disease) and 11 PRs (3, 42.8% and 8, 34.7%, respectively) with an ORR of 66.6% (71.4% and 65.2% respectively). The median duration of response in pts with metastatic disease was 8.5 mos and the overall Survival 14.5 mos (15 mos and 12.5 mos, respectively). Sixteen (53.3%) pts required a dose reduction and 5 (16.6%) 2 dose reductions. There were 4 episodes of febrile neutropenia and sepsis, which were successfully treated with broad spectrum antibiotics. There were no treatment delays due to myelotoxicity. G3/4 anemia and thrombocytopenia occurred in 12.5% and 9.3% of pts, respectively. G2 nephrotoxicity and G2/3 neurotoxicity occurred in 9.3% and 9.3% of pts, respectively. Alopecia was universal. G3/4 nausea/vomiting, G2/3 mucositis and G2/3 diarrhea developed 15.6%, 15.4% and 21.9% of pts, respectively. G2/3 fluid retention and G2/4 allergy occurred in 9.3% and 9.3% of pts, respectively.

Conclusion: The combination of EPI, DOC and CDDP is an active regimen for urothelial TCC, The safety profile mainly consisted of neutropenia leading to dose reduction, but with no serious infectious complications.

1407 PUBLICATION

Occupational prostate cancer risk factors in an area of coal, iron, and steel industries in Germany

T. Bandel[1], T. Reckwitz[2], S. Dickhut[1], P. Jedrusik[1,2], W. Weistenhöfer[1], H.M. Bolt[1], H. Schulze[2], K. Golka[1]. *[1]Institute of Occupational Physiology at the University of Dortmund, Dortmund; [2]Urological Department, Städtische Kliniken Dortmund, Dortmund, Germany*

Aim of the study was to identify possible risk occupations for prostate cancer in the Ruhr-area, a former center of the German coal, iron, and steel industries.

Methods: In 238 cases with histologically proven prostate cancer and of 414 controls with benign prostatic hyperplasia all occupations ever performed for more than 6 months and life time smoking habits of were asked for with a questionnaire. Confounder-adjusted odds ratios were estimated by Fisher's exact test and logistic regression analysis.

Results: Confounder-adjusted odds ratios for both age (OR 2.56) and duration of employment (OR 2.22) were elevated in underground hard coal miners. An elevated prostate cancer risk was also observed for painters/varnishers (OR 2.84 adjusted for age, OR 2.91 adjusted for duration of employment). Steelworkers showed no increased risk (OR 0.93 adjusted for age, OR 0.94 adjusted for duration of employment). Businessmen showed a remarkably low prostate cancer risk (OR 0.38 adjusted for age, OR 0.37 adjusted for duration of employment). No differences in the smoking habits described by pack years could be found between cases and controls.

Conclusion: Coal dust components and dietary factors due to high energy expenditure must be discussed as possible risk factors for prostate cancer in hard coal miners.

1408 PUBLICATION

Salivary biochemical and immunological profile following low-dose IL-2 based immunotherapy

R.M. Nagler[1], E. Gez[2], R. Rubinov[2], D. Laufer[1], H. Ben-Aryeh[1], D. Gaitini[3], M. Filatov[1], A. Kuten[2]. *[1]Oral Biochemistry Laboratory; [2]Dept. of Oncology; [3]Dept. of Diagnostic Radiology, Rambam Medical Center and Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel*

Purpose: One of the side effects accompanying low-dose recombinant interleukin-2 [rIL-2]-based immunotherapy is salivary hypofunction. We evaluated the functional and compositional whole salivary profile at both resting and stimulated conditions in 10 renal cell carcinoma patients who received prolonged low-dose rIL-2-based immunotherapy.

Results: At three days following the termination of four weeks of the combined administration of rIL-2 and rIFN-α, 21% reduction of salivary flow rate [$p < 0.05$] at resting condition was found, accompanied by significant multiple compositional alterations, including an increase in calcium, magnesium and phosphate concentrations by 65.6% [$p < 0.01$], 50% [$p < 0.05$] and 27% [$p < 0.05$], respectively, and a 23.5% [$p < 0.05$] reduction in the total protein concentration. In contrast, no flow rate reduction was noted under stimulated condition, and the only altered compositional component was the phosphate which was increased by 29.3% [$p < 0.05$]. The concentrations of all the other salivary components analyzed, including sodium, potassium, amylase, albumin, and the immunoglobulins, IgG, IgA and secretory IgA, were not effected by the immunotherapy. At one month following the termination of the immunotherapy, no functional or compositional salivary alterations were noted.

Conclusion: We recommend salivary-supporting therapies and anticariogenic treatments for patients undergoing low-dose rIL-2-based immunotherapy.

1409 PUBLICATION

Immunohistochemical evaluation of the apoptotic markers Bcl2, Par-4 and p53, VEGF receptor Flk-1 and correlation with clinicopathological parameters in localised prostate adenocarcinomas

A. Giannopoulos[1], L. Nakopoulou[2], E. Serafetinides[1], H. Gakiopoulou[2], A. Rashdan[1], A. Zervas[1], M. Giannopoulou[1], C. Dimopoulos[1]. *[1]Athens Medical School, University of Athens, Urology, Athens; [2]Athens Medical School, University of Athens, Pathology, Athens, Greece*

Purpose: Oncogenic protein Bcl2 expression is a key event in apoptosis while mutant p53 protein plays also an important role as it regulates expression of Bcl2. Prostate apoptosis response-4 (PAR-4) is specifically expressed by cells entering apoptosis. Flk-1 represents a high affinity receptor for vascular endothelial growth factor. In a retrospective study we evaluated the expression of the former markers in a cohort of 37 surgical specimens of localised prostate adenocarcinomas and the possible relationship with PSA, grade and stage.

Methods: Thirty seven formalin-fixed paraffin-embedded archival prostate cancer specimens were examined by immunohistochemistry with respect to apoptotic markers and Flk. Preoperative serum PSA, grade and pathological stage were included in statistical analysis.

Results: The expression of Par-4 and Flk-1 in malignant and normal prostatic tissue was inverse. No relation was found in expression of these markers with PSA, grade and stage. An inverse relation between p53 and Bcl2 expression with PSA was noted ($p = 0.0006$ and $p = 0.008$ respectively). Bcl2 expression in malignant tissue correlates with grade ($p = 0.044$) and stage ($p = 0.06$) of disease.

Conclusion: Bcl2 expression is considered an independent prognostic marker in early prostate cancer while corellation of the other markers needs further research.

1410 PUBLICATION

Gemcitabine and paclitaxel in previously treated patients with advanced transitional cell carcinoma

L. Marini[1], C. Sternberg[1], A. Sella[2], F. Calabrò[1], A. Van Rijn[1]. *[1]San Raffaele Scientific Institute, Medical Oncology, Rome, Italy; [2]Rabin Medical Center, Medical Oncology, Petah Tikvah, Israel*

Second-line therapy is needed for patients (pts) with transitional cell carcinoma (TCC) who fail first-line M-VAC chemotherapy. Both Gemcitabine (G) and Paclitaxel (T) have demonstrated activity in TCC. Based upon the results of an Q 2 week G + T schedule (Ann Oncol 1998; 9: 733–738), 18

pts with advanced and/or metastatic TCC, who had prior M-VAC were given G 2500–3000 mg/m^2 (in 30 min) and T 150 mg/m^2 (in 3 hrs). G-CSF was given on d 3–9 for >G 3 hematological toxicity. The median age was 67 years (range 46–76), with 15 males and 3 females. The median number of cycles was 8 cycles (range 2–14). 44% of pts had abdominal/pelvic masses, 55% had lymph node involvement (80% retro-peritoneal, 40% mediastinal, 30% pelvic), 33% lung mets, 11% hepatic mets, and 17% had bone mets. Of 16 bidimensionally measurable evaluable pts the overall RR was 50% (8/16) with 5 CR (31%) and 3 PR (19%). Two pts had SD, and 1 is too early. One pt with evaluable bone disease only had a marked reduction in bone pain for 4 months (mos). The MDR is 15 months (range 4–24+). One pt who attained a PR in the liver, died after the 14th cycle, due to GI bleeding and leukopenic sepsis. Alopecia was universal. Other grade 3/4 toxicities included: neutropenia in 7/18 pts (39%) and neurotoxicity in 1/18 (5%). G and T in pts with recurrent TCC can produce objective responses in pts who have failed M-VAC. An Q 2 week schedule appears to be well tolerated with acceptable toxicity. This study will be continued until 42 pts have been entered. G + T is a highly effective regimen in pts with advanced TCC who have failed prior cisplatin-containing chemotherapy.

1411 PUBLICATION

A Phase II study of the safety, pharmacokinetics and efficacy of IncelTM (biricodar, VX-710) in combination with mitoxantrone (M) and prednisone (P) in advanced hormone refractory prostate cancer (HRPC)

A. Einstein, Jr.[1], R. Lush[1], R. Rago[1], G. Bubley[2], W.D. Henner[3], G. Chatta[4], R. Shepard[5], E.A. Merica, M.W. Harding, W.S. Dalton[1]. [1]*Moffitt Cancer Center, Tampa, FL;* [2]*Beth Israel Deaconess Hospital, Boston, MA;* [3]*Oregon Health Sciences University, Portland, OR;* [4]*Arkansas Cancer Research Ctr, Little Rock, AR, United States*

IncelTM is a potent inhibitor of MDR mediated by P-glycoprotein (P-gp) and MRP expression. Analysis of prostate tumor specimens indicates a high incidence of MRP expression and a variable incidence of P-gp. Since mitoxantrone (M) is a P-gp and MRP transport substrate and prednisone (P) is a P-gp substrate, we initiated a Phase II study of Incel + M/P in HRPC patients (pts) in a 2 stage study design. Eight responses (>50% PSA decrease from baseline) in the first 20 pts supports enrollment to 59 pts in stage 2.

Endpoints: Primary – serum PSA response rate; secondary – duration of response, pain reduction, analgesic consumption and quality of life measures. Inclusion criteria: progressive HRPC (defined as new lesions, new disease related pain, or a 50% increase in PSA within 6 weeks of study entry); serum testosterone < 30 ng/ml; no prior chemotherapy; ECOG performance status 0–3; adequate organ function. Pts receive Incel (120 mg/m^2/hr) as a 72 hr CIVI with M (12 mg/m^2) administered 4 hrs after starting Incel and P (5 mg bid) administered throughout study treatment. Six pts received a course of M/P alone follow by Incel + M/P with intensive pharmacokinetics sampling. Pharmacokinetic analysis (n = 6) indicates that Incel does not significantly alter M clearance [median (range) of 0.35 (0.13–0.97) and 0.38 (0.11–0.54) L/h/kg for M/P alone and Incel + M/P, respectively]. As of March 1999, 26 pts have been enrolled and >75 courses of Incel + M/P have been administered. Incel + M/P has been well tolerated. Transient Gr 1/2 nausea & vomiting and Gr 1/2 nuetropenia are the principal treatment toxicities. Three pts experienced an uncomplicated febrile neutropenic episode, and 2 pts had consistent Gr 3 nausea/vomiting. Six pts discontinued prematurely. Among the other pts, 15/20 have completed >2 courses, 6 pts achieved partial responses with >80% sustained PSA reductions, 6 evaluable pts discontinued (4 with PD, 1 for Gr 3 ataxia, 1 death unrelated to study treatment) and 8 pts are too early to assess. The most current safety, pharmacokinetics and efficacy data for Incel + M/P will be presented.

1412 PUBLICATION

Myeloprotection of recombinant human granulocyte-macrophage colony stimulating factor (rhGM-CSF) given before MVAC regimen in patients with transitional cell carcinoma

C. Linassier[1], J. Hetroy[2], J.M. Boutin[1], P. Laplaige[3], O. Haillot[1], V. Lucas[4], L. Peyrat[1], C. Azema[5], Y. Lanson[1], P. Colombat[1]. [1]*CHU Tours, Oncology/Urology, Tours;* [2]*CH Chateauroux, Internal Medicine, Chateauroux;* [3]*Clinique, Blois;* [4]*CHR Orléans, Oncology, Orléans;* [5]*Schering Plough, Paris, France*

MVAC induces severe hematological and non hematological side effects. Recent in vitro data suggested that a short administration of GM-CSF before chemotherapy followed by 2 days without growth factor could protect marrow progenitors by inducing G0 state. In a phase II trial, we looked at the feasability of this type of administration before MVAC. 18 patients, 17 men, 1 women with a median age of 65.5 years (range 40–73) and transitional cell tumor were enrolled in the study. MVAC was given either as adjuvant (10 pts), neoadjuvant (3 pts) or metastatic (5 pts) therapy at the following dosage: MTX 30 mg/m^2/d d1, 15, 21, CDDP 70 mg/m^2 d2, ADR 30 mg/m^2 d2, vinblastine 3 mg/m^2/d d2, 15, 21. Patients received GM-CSF (Schering Plough R) 5 μg/kg/d for 3 days followed by a 2-day rest period before days 1, 15 and 21 of MVAC. 65 cycles were delivered (range 1–6). Mean relative dose intensity was 86% (33–100). One patient had fever and myalgia because of GM-CSF. Some cycles had to be delayed: 6/65 for hematological toxicity, 11/65 for non hematological toxicity. Treatment had to be stopped or modified in 8 patients, 3 for grade 4 hematological toxicity, 5 for extra hematological toxicity or progression. One patient died of purulent effusion during neutropenia.

These data suggest marrow protection by GM-CSF given before MVAC chemotherapy. Extra-hematological toxicity remained the major source of dose intensity reduction.

1413 PUBLICATION

Concurrent platinum and docetaxel chemotherapy and concomitant boost external radiotherapy for patients with invasive transitional cell bladder carcinoma (TCBC)

H. Varveris[1], M. Mazonakis[2], E. Lyraraki[1], S. Kachris[1], J. Damilakis[2], M. Koukourakis[1], D. Haldeopoulos[1], J. Velegrakis[3], J. Aerakis[2], Ch. Demetrakopoulos[3]. [1]*Dept. of Radiotherapy;* [2]*Medical Physics, University Hospital;* [3]*Dept of Urology, Venizelion Hospital, Iraklion, Crete, Greece*

Purpose: The present study evaluated the efficacy and toxicity of concurrent platinum and docetaxel chemotherapy (CT) with concomitant boost hyperfractionated (CBHF) radiotherapy for TCBC.

Material and Methods: 40 patients (33 males, 7 females) with clinical stages T1–4 invasive bladder carcinoma were treated after transuretheral biopsy and resection of the tumor, with (CT) and CBHF-radiotherapy. CAT-Scan and cystoscopy were most responsible for T-classification.

Chemotherapy, consisting of Cisplatin infusion (20 mg m^{-2}) and Docetaxel (20 mg m^{-2}) was given twice a week, simultaneously with irradiation, during the first 2 and the last 2 weeks of the whole treatment period (5 weeks). An external irradiation scheme (1.8–2 Gy per faction), 3 days a week, plus a CBHF radiotherapy regimen of 3.0 Gy, (1.8 Gy to the pelvis and 1.2 Gy to the bladder as a concomitant boost) was used concurrently with (CT). The CBHF-dose of 3 Gy was given combined to CT to take advantage of the radiosensitization with platinum and docetaxel compounds.

Results: All but 2 patients completed the planned chemoradiation protocol. The CR-rate assesed at 3 months after completion of combined treatment was 100%, 67%, 57% and 25% for clinical (c) stage, cT1 (8/8), cT2 (8/12), cT3 (8/14) cases, respectively. Eight of 38 patients (21%) relapsed locally and/or distantly, followed for 22.3 months (mean time). Thirty patients have no evidence of disease. The acute toxicity was estimated as moderate to severe; Myelotoxicity appeared in 20/38 patients while bebrile Grade III and IV neutropenia in two (5%) and thrombocytopenia (Grade I–III) in 5 (13%) patients respectively. The late effects were: one transient small bowell obstruction, one contracted bladder, Grade I–III hypersensitivity reactions in 4/38 (10%), stomatitis (Grade I–II) and Grade II skin reactions in two and three patients respectively. GM-CSF percutaneously and/or as enema solutions and amifostine (350 mg/m^2, 20 minutes before synchronous chemo-irradiation) were given prophylactically.

Conclusion: This preliminary analysis confirmed that the radiosensitizing effect of cisplatin and docetaxel to MV, CBHF- radiotherapy yielded a high CR-rate in TCBC patients with medium early (WHO) and late (RTOG) side effects. The value of such a combined treatment requires further evaluation because of the small number of patients, the short follow-up, and the absence of other studies using docetaxel as a radiosensitizer in urothelial cell cancer.

1414 PUBLICATION

Hormone-refractory prostate cancer (HRPC): Results of treatment with oral cyclophosphamide (CTX)

R. Nogueira-Costa, R.C. Duarte, L.A.G. Ramos, F.F.H. Bretas, O.J. Bicalho. *Oncocentro de Minas Gerais, Belo Horizonte, MG, Brazil*

Purpose: To evaluate the outcome of HRPC patients (pts) treated with CTX, all of whom had progressive disease after anti-androgen withdrawal. This subset of pts is known to carry a dismal prognosis.