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)

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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

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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)

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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)

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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.