

pts with advanced and/or metastatic TCC, who had prior M-VAC were given G 2500–3000 mg/m² (in 30 min) and T 150 mg/m² (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.

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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/m²/hr) as a 72 hr CIVI with M (12 mg/m²) 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 neutropenia 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.

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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 feasibility 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/m²/d d1, 15, 21, CDDP 70 mg/m² d2, ADR 30 mg/m² d2, vinblastine 3 mg/m²/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.

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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 transurethral 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 fraction), 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 assessed 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 febrile 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 bowel 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/m², 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.

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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.

Methods: Twenty-five evaluable HRPc pts with Karnofsky PS \geq 60% received CTX: 100 mg/m²/day \times 10 every 3 weeks. Evaluation criteria of response: serum PSA and measurable disease. Median pre-CTX PSA level: 42.6 ng/ml (range: 0.6–761.0 ng/ml); 3 pts had normal PSA. Age range: 54–87 years (median: 73 yrs).

Results: With a median follow-up of 10 months (mo), range: 2–31 mo, we obtained 5 (20.0%) complete remissions (CR) with a median duration of 15 mo (range: 5–22 mo); 5 (20.0%) partial remissions (PR) lasting 3 to 20 mo (median: 6 mo); 5 (20.0%) stable diseases (SD), with a median duration of 6 mo (range: 1–7 mo) and 10 (40.0%) progressions (P). Median overall survivals after initiation of CTX were: CR: 27 mo (range: 6–31 mo); PR: 13 mo (range: 4–29 mo); SD: 8 mo (range: 3–16 mo); P: 9 mo (range: 2–15 mo). There were no deaths among CR, PR, and SD pts; 60.0% of P pts died of active HRPc. Number of CTX cycles to achieve objective response (CR + PR): 5 (range: 1–15). Toxicity was mild and well tolerable. (To be presented).

Conclusions: CTX is an efficacious and well tolerated treatment for HRPc pts. This may reflect in an apparent improvement of survival and quality of life of objective responders.

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PUBLICATION

The accuracy of patient positioning in irradiation of prostate cancer by portal film analysis

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Purpose: Portal imaging is used for quality assurance of radiotherapy treatment fields. We analyzed retrospectively the accuracy of treatment delivery in 34 prostate cancer patients (pts) treated by 4 field technique (BOX) pelvic irradiation followed by boost arc therapy, and in 25 pts treated by 4 "small" pelvic fields.

Methods: We compared weekly portal images to digitized simulation films using a computer assisted quality assurance program (PIPSpro, Masthead Canada) using fiducial points and contrast improvement filters technique to determine overdose and underdose of each portal film.

Results: Pelvic fields portal films of 34 pts (194, 97 AP-PA, and 97 lateral) were analyzed. The mean equivalent square field size was 16×16 cm² in AP-PA and 14.2×14.2 cm² in lateral. The average overdose area (AOA) was 2.75% (range 0.08–14.05), and average underdose area (AUA) was 2.74% (range 0.03–23.92) in AP-PA portals. In the lateral portals it was 2.49% (range 0.21–16.03), and 2.78% (range 0.29–29.55) respectively. Portal films of 25 pts (194, 98 AP-PA, and 96 lateral) treated by small fields were analyzed. The mean equivalent square field size was 10.6×10.6 cm² in AP-PA and 10.3×10.3 cm² in lateral. The AOA was 0.88% (range 0.00 \times 2.80), and AUA 0.86% (range 0.00–2.70) in AP-PA portals, 1.03% (range 0.10–3.80), and 0.82% (range 0.00–2.40) in lateral portals.

Conclusion: The accuracy of prostate cancer patient positioning in our institution is in the range of 25% for large fields, and 1.0% for small fields.

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PUBLICATION

Rational mutagenesis of a recombinant anti-tumour antibody

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Purpose: C595 monoclonal antibody (an anti-MUC1 mucin antibody) and its fragments are currently being used to image superficial bladder tumours. To promote greater understanding of how C595 interacts with MUC1, molecular modelling, site-directed mutagenesis and standard immunoassays have been utilised to probe the antigen binding pocket

Methods: A model of C595 variable fragment (Fv) was produced using homology modelling. Residues of suspected importance in antigen recognition were selected for mutagenesis. Oligonucleotide directed mutagenesis was employed to produce mutations, and mutants were expressed in *E. coli*. ELISAs were performed to analyse effects of mutations on association and dissociation to MUC1.

Results: Ten mutant Fvs have been produced, each with differing relative affinities for MUC1. Mutations of Asp to Asn within the pocket yielded much longer association rates (H97DN, H100DN & H95DN have 22%, 64% and 87% of parental Fv association rate respectively), while a mutation of Asn to Asp in the pocket gave a longer relative dissociation rate (L93ND – 24% increase on parental rate). Some mutations had no appreciable effect on the antibody-antigen interaction.

Conclusion: Molecular modelling coupled with site-directed mutagenesis of an antibody binding pocket is a powerful tool for examining the antibody/antigen interaction. This study has scrutinised the antibody pocket for important residues involved in the interaction with MUC1 and has provided new lead entities for use as radio-imaging/therapy agents in bladder cancer.

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PUBLICATION

Radiation therapy for Peyronie's disease

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Purpose: To retrospectively analyse treatment outcome in patients (pts) irradiated for Peyronie's disease (PD).

Methods: The radiotherapy (RT) records of pts irradiated for PD between 1982 and 1997 were reviewed. The RT schedule consisted of 13.5 Gy (9×1.5 Gy, 3 fractions per week) using orthovoltage in 138 pts, or 12 Gy (6×2 Gy, daily fractions) using electrons in 39 pts. RT schedule was not clearly reported in 2 pts.

Results: Of the 179 pts (median age 52 years), 78% presented with painful erections and 89% with penile deformity. The symptoms were present for a median duration of 6 months (range 1–72 months) prior to RT. 17% of pts had been previously treated (unsuccessfully) with other methods. Fibrous plaques were dorsally localized in 95% of pts and had an average surface of 3.3 cm² (range 0.5–18 cm²). No RT related complications were reported except for transient dysuria in a single pt. Of the 139 pts who attended follow-up at a mean of 3 months (range 0–13 months), 71% reported that their pain was diminished or had disappeared. 21% of pts reported a decrease in their penile deformity. From a questionnaire mailed to 139 pts it was found that 72% were sexually active, 48% complained of erectile dysfunction and 49% were dissatisfied with their current sex life.

Conclusion: Low dose external RT (12–13.5 Gy) appears to be an effective treatment in pts with PD who have persistent complaints of painful erections. No significant RT associated morbidity is seen with such doses.

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PUBLICATION

Detection of bladder cancer by qualitative determination of human complement factor H-related protein (hCFHrp) in urine

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The purpose of this study was to assess a new qualitative urinary tumor marker for transitional cell carcinoma of the urinary bladder (TCC), human complement factor related protein (hCFHrp).

Urine samples of 298 individuals were examined for the presence of the human complement component H related protein (hCFHrp), using the BTA STAT test. The control group included 76 healthy volunteers and 110 patients with benign urologic diseases. The study group consisted of 82 patients with histologically proven bladder cancer. Samples of all patients were obtained prior to therapy.

hCFHrp was positive in 66/82 samples of patients with histologically proven bladder cancer (sensitivity: 80.5%). Sensitivity was dependent on tumor stage (pTa: 36.4%, pT1: 92.9%, pT2: 94.1%, pT3: 100%, pT4:100%). All patients with pT1G3 tumors were identified by the test. hCFHrp was negative in all healthy individuals (specificity 100%). In contrast, 58/110 hCFHrp determinations in patients with benign urologic disorders were false positive, resulting in an overall specificity of 72%.

We therefore conclude that hCFHrp is a sensitive marker for detection of bladder cancer and for identification of patients at high risk. BTA STAT is thus potentially useful for follow-up-studies in patients in whom benign disorders of the urinary tract can be excluded.

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PUBLICATION

Metastatic renal cell carcinoma: A new approach with combined radioimmunotherapy

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Purpose: Patients with secondary bone metastases from renal cell carcinoma (RCC) have a poor prognosis. The presented radioim-