809 POSTER

Use of MOSFET detectors for in-vivo dosimetry during permanent low-dose-rate prostate implants

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Purpose: Prostate volume and shape can change during trans-perineal interstitial permanent prostate brachytherapy due to edema caused by the trauma of needle insertion, making it difficult to achieve the planned implant geometry and hence the desired dose distribution. An instant in-vivo dose measurement device would be useful to facilitate adjustment of the seed distribution in response to changing geometry during the implant procedure.

The purpose of this work was to evaluate specially designed MOSFET detectors for in vivo dosimetry inside the bladder and along the urethra immediately post-implant.

Materials and Methods: The detectors used for the in vivo measurements were dual Metal Oxide Semiconductor Field Effect Transistors (MOSFETs. Angular response of the MOSFETS was measured in the 100 kVp orthovoltage beam, which has an effective energy similar to that of the 125I seed. Calibration in terms of dose per unit response of the detector was done in a solid water phantom using a special high activity 125I seed. Prior to use for in-vivo measurements all MOSFETs were sterilized. MOSFET detector was inserted into the lumen of the Foley catheter. Measurements were taken at 1 cm intervals from base to apex of the prostate. For each measurement point, the distance between the MOSFET and the lower edge of the Foley balloon was recorded to provide the reference to the internal bladder wall.

Results: We have performed the measurements of the initial dose rate along the urethras of several patients. The dose rate increased with the distance from the bladder, reaching a maximum inside the prostatic part of urethra. The value of this maximum for different patients ranged from 10 to 16 cGy/hr, corresponding to the total absorbed dose of 205 to 328 Gy. The shape of this dose rate curve can help to evaluate an overall implant quality. The in-vivo measurements agreed well with the post-implant treatment plan calculations.

Conclusions: Specially designed MOSFET detectors are very useful for in vivo dosimetry of permanent prostate implants. When inserted into the urethra, they can measure in real time the initial dose rate received by this organ. This can serve not only as an indicator of possible treatment complications due to excessive dose to the urethra, but also as a measure of the overall quality of the implant.

810 POSTER

Pulmonary migration of permanent interstitial sources in patients undergoing prostate brachytherapy

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Purpose: Permanent prostate brachytherapy can be performed by a number of techniques, of which the most popular are the pre-plan method using linked sources and the real-time method using loose seeds deposited by an applicator. An inherent advantage to the strand method has been the potential to reduce seed migration to the lung. When CXR were taken the day after the procedure Tapen found an incidence of 0.7%(Int J Rad Oncol Biol Phys 42:1063, 1998). A study with longer follow-up in patients treated with linked sources, found 25% with at least one seed in the lung(Merrick et al, Int J Rad Oncol Biol Phys 46:215, 2000). To date, the incidence of pulmonary migration of seeds has not been reported with the real time technique.

Methods: 238 patients were implanted with either I-125 (146) or Pd-103 (92). Patients were implanted with the real time method using the Mick applicator to place the sources. The implant was peripherally based (75%) and care was taken to place the sources just underneath the prostate capsule rather than outside of the gland. Post-implant dosimetry was performed at 1 month. Following implantation, routine chest x-ray (CXR) was obtained at a minimum of 3 months post implant. 24 patients had a second CXR.

Results: Of the 238 patients 141 (59%) had stage < T2b and 175 (73.5%) had Gleason score < 7. The median PSA was 7.5 ng/ml (range 1.3-124), 118 (50%) were treated with 6-9 months of hormonal therapy and 39 (16.4%) had a combination of implantation and external beam irradiation. A total of 21,654 seeds were implanted (median 89, range 27-220). Post-implant CXR were obtained at a median of 912 days (range 147-3023). Of the 238 patients, 4 (1.7%) experienced at least one seed embolus to the lung. 10/21654 (0.005%) seeds were found in the lungs. All 4 patients had received an I-125 implant, giving the pulmonary embolus rate for I-125 at 4/146 (2.7%) and for Pd-103 0/92. No patients experienced a subsequent seed migration if it was not seen on the initial film. The median D90 for all I-125 was 172 Gy and for the 4 with migration was 174 Gy.

Conclusion: Seed embolism to the lungs is a rare event when patients are implanted using the real time method. The most likely explanation for the low migration rate is that the sources are placed just inside of the capsule rather than outside of the prostate. While migration appears to be slightly higher with I-125 compared to Pd-103, there is no negative effect on post-implant dosimetry results.

811 POSTER

Intravenous vinorelbine (i.v.VRL) and estramustine (EMP) in patients (pts) with androgen-independent prostate cancer (AIPC): final results

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Purpose: The single-agent activity of both i.v.VRL and EMP is well established in AIPC. The two-drug combination formed then the basis for a phase II trial. The main objective was to assess clinical efficacy and tolerance of i.v.VRL in combination with oral EMP in pts with AIPC previously untreated by chemotherapy.

Methods: From 1996 to 1999, 51 pts with Karnofsky PS * 60% and median age= 69 years, were included. They were given i.v VRL (25 mg/m* i.v. (D1-D8) every 3 weeks) and EMP (600 mg/m* continous oral daily). PSA response represented the main evaluation criterion. Tumour response in pts with measurable disease and clinical benefit were evaluated.

Results: A median of 5 administrations was given. The median relative dose intensity was 98.1% for VRL and 98.2% for EMP. Decrease in PSA by >50% and >80% were seen in 41% and 33.3% of the pts, respectively. Out of the 7 pts with measurable disease, two (28.5%) had a partial response, and out of the 36 evaluable pts for clinical benefit, disease control (responder + stabilisation) was observed in 66%.The median progression free survival was 4.7 months, and the median survival was 14.3 months. The toxicity was acceptable. Neutropenia grade (3-4) was seen in only three pts (6.1%). Thrombocytopenia (grade 4) occurred in 1 patient (2%).Thirteen pts (25.5%) experienced vomiting (< grade 3), nausea (< grade 3) was observed in 28 pts (24%). Thrombotic complications (grade 3-4) occurred in 2 pts (4%). Cardiac dysrythmia(grade 4) and cardiac ischemia (grade 4) were reported in 3 pts (1.1%). Three pts (1.1%) experienced (grade 3) cardiac dysfunction.

Conclusions: The present study showed that i.v.VRL in combination with EMP is an effective regimen in pts with AIPC previously untreated by chemotherapy. VRL can be administered safely in combination with EMP. Further clinical studies especially with various schedules and doses of estramustine are warranted.

812 POSTER

Association of a G915C (ARG25PRO) polymorphism of the TGF-beta1 gene with prostate cancer

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Purpose: Links between disease susceptibility and genetically determined variation in human cytokine expression have recently been described. Transforming Growth Factor-b1 (TGF-beta1) plays an important role in the regulation of growth and differentiation of prostatic cells. A Gà C transition at nucleotide 74 of the TGF-beta1 gene results in a Argà Pro substitution at amino acid 25 of the signal peptide. We have examined a possible association of TGF-beta1 genotype with prostate cancer.

Methods: Blood samples were obtained from 51 healthy male blood donors (HD), and 50 prostate carcinoma patients (PC). DNA was extracted from the blood samples through salting-out. The polymerase-chain reaction (PCR) allowed the genotyping of the samples in G915C using two sets of primers describe previously by other authors: each set amplified the gene containing the G or the C nucleotide.

Results: We found that 45% (23/51) of the HD were heterozigotes, presenting a CG genotype; all the other HD presented a GG genotype. Only 14% (7/50) of the PC were heterozigotes, with all the other patients presenting the GG genotype.

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