

Expansion to the first Efficacy Stage has commenced and Pilot Phase safety data will soon be known.

4028

POSTER

Current outcomes of clinical trials in carbon ion radiotherapy for prostate cancer

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Background: Carbon ion radiotherapy (C-ion RT) is characterized with better dose concentration and higher biological effect than photons. Three prospective clinical trials of hypofractionated C-ion RT for prostate cancer were performed at our institute since June 1995. The recommended dose-fractionation and treatment methods were established through two dose-escalation trials and validated by the following phase II trial.

Methods: Patient with previously untreated, biopsy proven adenocarcinoma of the prostate without metastasis was eligible for the trials and a total of 461 patients were treated until August 2006. Of those, 96 patients received the C-ion RT in the two consecutive phase I/II trials until March 2000. Radiation dose was escalated from 54.0 GyE up to 72.0 GyE in 20 fractions and the recommended dose of 66.0 GyE was obtained from the result of these dose-escalation trials. The following 365 patients received the C-ion RT with the recommended dose in the phase II trial and were analyzed in this study. Androgen deprivation was applied to the intermediate and high-risk patients combined with C-ion RT and low-risk patients received only C-ion RT. Primary endpoint of this study was biochemical relapse free rate (BRF) and the secondary endpoints were late radiation toxicity and disease specific survival (DSS). Biochemical failure was defined as 2.0 ng/ml increase from the nadir according to the new criteria of the American Society of Therapeutic Radiation and Oncology (ASTRO).

Results: No patient was lost to follow up and median follow up period of 365 analyzed patients was 38.3 months. Twenty-nine patients developed biochemical failure and 5-year BRF of entire group was 89.6%. Only four patients have died of prostate cancer so far and the 5-year DSS of the entire group was 98.2%. Clinical stage and centrally reviewed Gleason score were significant prognostic factors for both BRF and DSS. No grade 3 radiation toxicity was observed and the incidences of grade 2 rectal and genitourinary (GU) toxicities were 1.4% and 3.6%, respectively.

Conclusions: Sufficiently safe and effective treatment option using hypofractionated C-ion RT could be established.

4029

POSTER

Phase II clinical trial of metronomic cyclophosphamide (CTX) plus celecoxib (C) and dexamethasone (DEX) in advanced hormone refractory prostate cancer (HRPC): preliminary clinical and pharmacodynamic results

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Background: Low-dose metronomic CTX and C have demonstrated a significant antiangiogenic activity in preclinical studies. Moreover, a single infusion of maximum tolerated dose chemotherapy, given before metronomic treatment, can increase its antiangiogenic activity.

Methods: A total of 27 patients (pts) with advanced HRPC received CTX 500 mg/sqm iv day 1 and CTX 50 mg po daily, DEX 1 mg po daily and C 200 mg po BID continuously, starting from day 2. Primary end point was activity (PSA reduction >50%); secondary were: objective responses, toxicities (NCI-CTC criteria), PFS, OS, evaluation of plasma levels of thrombospondin-1 (TSP-1), VEGF, sVEGFR-2, VE-cadherin mRNA; expression and synthesis of TSP-1 and VEGF in peripheral blood mononuclear cells. Pts characteristics: median age 74.5 years (54–91), median PS 1 (0–2), median baseline PSA 73 ng/ml (9.69–>5000); main sites of disease: bone 22 pts (81.5%), lymphnodes 10 pts (37%); previous chemotherapy 20 pts (74.1%).

Results: 27 pts are evaluable for toxicity and response. Overall PSA decrease ≥50% was found in 9 pts (33.3%). Median time to PSA progression was 3.2 months (95% CI 2.7–3.7 months) and median OS was 20.9 months (95% CI 14.5–27.3 months). No G3–4 hematologic or non-hematologic toxicities have been observed. Preliminary pharmacodynamic data indicate that a significant difference was observed in TSP-1 and VEGF levels between responders and non responders pts at day 84 of treatment. Indeed, the responders showed a significant increase of TSP-1 plasma concentrations (163.7±22.3% at day 84 vs. 100% at day 0; P<0.05) and a concomitant significant decrease of plasma VEGF levels (29.8±11.7% at

day 84 vs. 100% at day 0, P<0.05), whereas the non responders showed a marked increase of both plasma TSP-1 and VEGF levels.

Conclusions: Metronomic chemotherapy with CTX plus DEX and C in pts with HRPC showed promising activity without relevant toxicity; interestingly, patients who responded to this metronomic schedule showed a concomitant increase of the endogenous inhibitor of angiogenesis and a decrease of a pro-angiogenic factor.

4031

POSTER

Pretreatment international prostate symptom score correlates with postbrachytherapy erectile dysfunction

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Background: To determine the factors that may predict for erectile dysfunction (ED) following prostate brachytherapy based on use and reported effectiveness of phosphodiesterase-5 inhibitors (PDE-5i)

Materials and Methods: 95 patients with T1c-T2c prostate cancer who underwent low-dose rate TRUS-guided brachytherapy +/- external beam radiation therapy (EBXRT) were retrospectively analyzed. Minimum follow-up = 12 months. Post-implant CT scans were performed 4–6 weeks following implant for dosimetry. Patients were asked about the use and effectiveness of any PDE-5i both prior to initiation of any therapy (brachytherapy or EBXRT) and on follow-up. Each patient was given an erectile function (EF) score (between 0 and 5) based on the scale in Table 1.

EF Score Definition

Score	Description
5	Normal EF; No PDE-5i use
4	EF sufficient for intercourse (IC) +/- PDE-5i
3	EF sufficient for IC only with PDE-5i, 100% efficacy
2	EF sufficient for IC with PDE-5i, but <100% efficacy
1	EF insufficient for IC even with PDE-5i
0	No EF or spontaneous erections (e.g., penile implant)

Results: The patients had a median follow-up of 27.4 months after brachytherapy. Median age was 66.5 years. There were 43 Caucasians and 52 African-Americans. Eighteen patients received adjuvant androgen ablation (AA) for a minimum of 4 months; 39 received supplemental EBXRT. Sixty-two had a history of smoking, 26 had diabetes mellitus (DM), and 71 had hypertension (HTN). The International Prostate Symptom Score (IPSS) prior to therapy ranged from 3 to 17 (median = 7). The median EF score before any therapy (EFpre) was 4 and after treatment (EFpost) was 3. A significant association was found between the decrease in EF score and AA (p=0.0002) or DM (p=0.009). In a multivariate analysis, there was a significant association between EFpost (adjusting for EFpre) and smoking history (p=0.003), EBXRT (p=0.002), prostate D90 (p=0.035), prostate V100 (p=0.014), and IPSS (p=0.001); there was no correlation between EF and age, race, T-stage, initial PSA, Gleason Score, AA, DM, prostate volume, # seeds, or isotope. A multivariate logistic regression model of EF was obtained by dichotomizing EF groups into EF=1 (EF scores 3, 4, 5) and EF=0 (EF scores 0, 1, 2). We found that prostate D90 >110% (adjusting for EBXRT, smoking, prostate V100 and IPSS) significantly increased the risk of ED (odds ratio = 8.7, confidence interval = 1.4–52.2); similarly, IPSS >7 significantly increased the risk of ED (odds ratio = 6.7, confidence interval = 2.3–18.9). A bivariate analysis of EFpost by IPSS determined the following correlation: EFpost = 4.85 – 0.25 × IPSS. **Conclusions:** Patients with high IPSS on presentation have a significantly higher risk of reduced PDE-5i effectiveness, and hence ED following brachytherapy. Prostate D90 and V100 may be surrogate predictors of potential normal tissue injury to structures (e.g., neurovascular bundles) in the periphery of the prostate gland.

4032

POSTER

Hypofractionated conformal radiotherapy for good prognosis carcinoma of the prostate: seven year outcome analysis

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Background: The optimal external beam radiotherapy dose and fractionation in the radical treatment of localised prostate cancer continues to be investigated. This includes not only dose escalation using conventional

fractionation, but also the exploration of hypo-fractionated regimes for prostate cancer given its suggested low α/β ratio. We report the long term efficacy of radiotherapy using a hypo-fractionated 50 Gy in 16 fractions (3.13 Gy per fraction) in men with localised prostate cancer.

Materials and Methods: A retrospective review of men with localised prostate cancer treated consecutively with conformal radiotherapy at a single institution between January 1995 and May 2001 was performed. Only patient's in the good prognostic group (PSA \leq 10 ng/ml and Gleason \leq 6 and Clinical stage T1/2) were included in the study. A conformal external beam radiotherapy dose of 50 Gy in 16 fractions over 22 days was delivered using a 4 field arrangement on a linear accelerator with energy \geq 6MV. The planning target volume (PTV) was defined as GTV (Prostate \pm base of seminal vesicles) + 1 cm in all directions except posteriorly were 7 mm was used. Patients treated with neo-adjuvant, concurrent or adjuvant hormonal therapies were excluded. Biochemical failure was defined using both the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus definition and Phoenix definition (Nadir + 2 ng/ml).

Results: One hundred and ninety-nine men were identified. 73 with clinical T1 and 126 with clinical T2 disease at presentation. The median age at presentation was 67.9 years (49.9–81.6 years) and median initial PSA was 5.9 ng/ml (0.1–10 ng/ml). Histological review demonstrated that 78, 49 and 72 patients had Gleason scores of 4, 5 and 6 respectively. At a median follow-up of 84 months (4.6–134.9 months), the 7 year actuarial overall survival was 83.2% and the biochemical failure free survival was 55% and 76.8% as defined by the ASTRO consensus and Phoenix definitions respectively.

Conclusion: This data demonstrates the efficacy of a hypofractionated regime for good prognosis patients. It provides similar levels of biochemical control when compared with other reported long term outcomes with conventional radiotherapy fractionation (2 Gy per fraction).

4033

POSTER

Preliminary results of late rectal and urinary toxicity in a phase II randomized study of conventional fractionation vs. hypofractionation on patients with high risk prostate cancer

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Background: Several recent studies suggested a great sensitivity of prostate cancer to high dose fractions due to an estimated α/β ratio of 1.5–2 Gy. With estimated α/β values of 3 to 5 Gy in late responding normal tissues of the pelvis, theoretical modeling shows a stronger enhancement of tumor effect than of late complications for larger (and fewer) fractions in prostate tumours. The purpose of this study is to test this hypothesis by comparing the late complication rate of a conventional fractionation and a biologically equivalent hypofractionated regimen in the radiotherapy of prostate cancer.

Material and Methods: From January 2003 to March 2007, 144 patients with histologically proven, high risk prostate cancer were recruited to this study. All patients received a total androgen deprivation (AD) for 9 months. A 3D conformal radiotherapy to prostate and seminal vesicles was started after two months of AD. Patients were randomized to receive 80 Gy in 40 fractions in 8 weeks (control arm A) or 62 Gy in 20 fractions in 5 weeks, 4 fractions per week (hypofractionation arm B). Late toxicities were defined as those detected 6 or more months after the end of radiation treatment, and were evaluated following the EORTC/RTOG score system. The rectal mucosa damage was also evaluated in all patients with a 3 grade score scale (slight edema and rare telangectasia, moderate edema and confluent telangectasia, and necrosis) by means of pre- and post-treatment recto-sigmoidoscopies performed every six months after the end of radiation treatment.

Results: One hundred thirty seven patients with a follow-up longer than 6 months, 70 in the control and 67 in the hypofractionation arm were evaluated for late toxicity. Grade \geq 3 toxicity was experienced by 4 patients of arm A, 2 (1.5%) rectal and 2 (1.5%) urinary toxicity, and in 1 patient of arm B (1.5%) who experienced an urinary incontinence. The actuarial 2-year $G \geq 2$ late rectal toxicity was 11.6% and 12% in the hypofractionated and control arm, respectively ($p=0.89$). The actuarial 2-year $G \geq 2$ rectal mucosa damage was 18% and 20% in the former and latter arm, respectively. The actuarial 2 year $G2$ late urinary toxicity was 2.3% and 9.3%, respectively, for the experimental and control arm, respectively ($p=0.2$).

Conclusions: From these preliminary results, the hypofractionation schedule seems to be as safe as the conventional fractionation for both rectal and urinary tissues, with a slight but not significant trend in favor of hypofractionation, thus confirming the hypothesis of the theoretical modeling.

4034

POSTER

High or low dose rate in the radiation treatment of prostate cancer: different results and toxicity rates?

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Background: to analyse results after shifting from low dose rate (LDR) brachytherapy (BT) to high dose rate (HDR) treatment as a boost to external beam radiotherapy (EBRT).

Materials and Methods: From 1997 to 2005, 328 patients with locally advanced prostatic adenocarcinoma were consecutively and prospectively treated with BT as a boost to 3D conformal EBRT. All over the study, BT techniques remained unchanged unless dose delivery. Until 07/2002, 201 patients received 40 Gy EBRT and a 42 Gy LDR BT boost with 192Ir wires. Afterwards to introduce the stepping source technologies, we shifted to a HDR BT boost for the last consecutive 127 patients. To shorten BT procedures, we delivered only one fraction of 10 Gy while increasing the EBRT dose up to 60 Gy to maintain a same Extrapolated Response Dose (ERD) of 143 Gy3. The ERD to the 20% most anterior region of the rectum were thus 126 Gy3 and 117 Gy3, respectively for the HDR and LDR patients.

Results: The median follow up are 60 months for the LDR group and 31 months for the HDR group. No difference in initial prognostic factors was present (initial PSA, Gleason score, clinical Stage) between the two groups of patients. Recurrence rates of 23% and 27% at 33 months are not different ($p=0.88$). However, late severe grade 3 rectal toxicity at 2 and 3 years are respectively 2.36% and 3.15% for the HDR group but 0% for the LDR group ($p=0.01$).

Conclusions: With identical EBRT and BT techniques and a same 143 Gy3 dose, the control rate of the disease at 31 months was similar in the two different groups. Our experience confirms thus the low α/β ratio of prostatic adenocarcinoma. However, rectal toxicity was significantly greater in the HDR arm. So, as opposed to what is commonly believed when the α/β of a tumor is low, shifting from LDR to hypofractionation can be similar in terms of disease control but not in terms of late toxicity. This observation can have significant impact on designing future protocols based on hypofractionation.

4035

POSTER

Effect of comorbidity on overall survival in patients with prostate cancer

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Background: The use of biochemical failure free survival in prostate cancer is controversial because mortality due to other causes is not taken into account. The aim of this study is to evaluate the impact of age and comorbidity on the overall survival (OS) and calculate the relative survival, which is important for patient counseling and clinical decision making.

Materials and Methods: All patients were selected with localized (T1–3NX-0M0) prostate carcinoma primarily treated with curative radiotherapy in our hospital between 1991 and 2000. Information on T-, N- and M-stage, age, performance score, Gleason score/grade, PSA-value, comorbidity and prior malignancies was abstracted from the charts. Comorbidity was measured using the Adult Comorbidity Evaluation index (ACE-27). The prognostic value of these variables on OS and disease specific survival (DSS) was studied. The OS of the patients was compared to an age- and period matched cohort of men from the Dutch population.

Results: Of the 395 patients treated, 217 died after a median follow up of 6.0 years, 94 due to prostate cancer, 30 due to other tumors, 66 due to intercurrent disease, and in 27 the cause of death was unknown. 130 patients developed a recurrence: 119 distant metastases, 27 loco-regional recurrences.

Mean age at diagnosis: 70.2 years (SD 6.2), median pretreatment PSA level: 19.0 ng/ml. The median radiation dose was 66 Gy (60–70 Gy). 18.7% received hormonal therapy during RT. The ACE-27 score was 0 in 38.9% of the patients, 1 in 22.2%, 2 in 24.1%, 3 in 3.8%. T1: 13.9%, T2: 54.2%, T3: 31.9%. Grade 1: 26.8%, 2: 46.3%, 3: 23.5%. 47 prior malignancies were found in 43 patients (10.9%).

The 5-year OS was 74.2%, the 5-year DSS 83.4%. ACE27, age, grade and PSA were independent prognostic factors for OS. The mean OS was 8.9 years compared to 10.1 years for the matched controls ($p<0.0001$). Relative survival analysis showed excess mortality in the third to tenth year of follow up of $\pm 2\%$ per year. For the low/intermediate risk group and patients aged >80 years no excess mortality was seen. In the age group 71–80 excess mortality started after 6 years.

Late grade 3 or 4 complications of the rectum were found in 18 patients (4.6%), of the bladder in 24 patients (6.1%).