Conclusion: IMRT based on sentinel lymph node identification is feasible and allows pronounced normal tissue sparing. The probability of a 'geographic miss' is reduced. We are planning a prospective trial with dose escalation to the prostate (74−78 Gy) continuing the presented treatment regime.

4025 POSTER

A phase I/II study of sunitinib in combination with docetaxel (dcx) and prednisone (pdn) in patients with metastatic castrate-resistant prostate cancer (mCRPC)

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Background: Sunitinib malate (SUTENT®) is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET and FLT3. VEGFR and PDGFR overexpression are implicated in prostate cancer progression and bone metastasis, respectively; thus, co-administration with sunitinib may improve the antitumor activity of dcx. The objectives of this ongoing phase I/II study are to determine the optimum combination dose (OCD), safety and PK profile of sunitinib combined with dcx + pdn as first-line treatment for mCRPC.
Methods: All pts received a lead-in of sunitinib 50 mg/d for 4 wks to obtain preliminary data on PSA modulation by sunitinib alone. To date, 3 successive cohorts have received dcx 60 mg/m^2 every 3 wks + pdn 5 mg BID and escalating sunitinib doses (cohort 1: 12.5, 2: 37.5, or 3: 50 mg/d) on a 2 wks on/1 wk off schedule. A final cohort 4 (ongoing) is receiving dcx 75 mg/m^2 + sunitinib 37.5 mg/d + pdn 5 mg. DLTs are evaluated during the first 3-wk combination cycle. PK profiles for sunitinib and its metabolite, SU12662, are obtained on day 1 of the lead-in period and day 1 of cycle 2 (with dcx). PK profiles for dcx are obtained on day 1 of cycle 1 (dcx alone) and day 1 of cycle 2 (with sunitinib). Preliminary efficacy is assessed per the PSA Working Group Criteria and RECIST.
Results: Twenty-three pts have enrolled in the 4 cohorts (n = 6, 7, 6 and 4, respectively). To date, 6 pts discontinued due to disease progression and 6 due to AEs; 1 pt died due to disease progression. Three pts have completed 1 year on study and are eligible to enroll in a sunitinib continuation protocol. The median durations of treatment in cohorts 1 and 2 were 6.3 and 6.6 months, respectively. The most common treatment-related AEs were neutropenia (70%), fatigue (44%), anorexia (30%) and diarrhea (30%). Only 1 DLT was observed, a grade 3 hyponatremia in cohort 3. Confirmed PSA response occurred in 9 (39%) pts and objective response in 3 (13%) pts, each with confirmed partial response. At the time of the data cutoff, 2 additional pts had reached a partial response, although unconfirmed.
Conclusions: Sunitinib in combination with dcx + pdn appears to be safe and well-tolerated. Based on these results, the OCD was chosen as sunitinib 37.5 mg/d in combination with dcx 75 mg/m^2 and pdn 5 mg BID. The study is now proceeding to phase II to further assess the safety and efficacy of this regimen in the first-line treatment of mCRPC.

4026 POSTER

Clinical implementation of a novel method of image guided radiation therapy (IGRT) of prostate cancer by "localization of intrinsic isocenter" and "dynamic margin" – retrospective analysis of 3370 adaptive IGRT deliveries using an in-room CT on rails system

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Purposes/Objective: Prostate movements throughout radiation treatment course can be a combination of (a) systematic set up error – the prostate position reverting to the "intrinsic isocenter" which is different from the initial CT simulation isocenter – and/or (b) random error – daily variance of the prostate positions from its intrinsic isocenter.
We developed a novel method of adaptive targeting to localize the "intrinsic isocenter" and to minimize the random errors by varying the treatment margins using a dynamic margin.
Methods and Materials: A total of 3370 IGRT treatment for prostate cancers from 2000 to 2006 formed the basis of this study. The first group – 284 patients had 5 IGRT fractions each. They form the 'no shift' group. The second group – 114 patients had 10 IGRT fractions. The third group of 54 patients had 15 IGRT fractions.
In this approach, the mean and variation of isocentre shift is reviewed after each 5 IGRT fractions. The isocentre was shifted accordingly if the observed "intrinsic isocenter" deviated from its planned position with more than 2 mm. The set up variation with respect to the new intrinsic isocenter is subsequently estimated in each of the next 5 IGRT fractions. The entire setup error data is formed as the basis of "dynamic margin" and updated intrinsic isocenter for the reminding 28 IMRT fractions. This approach follows the "observe-adjust-evaluate" loop method and was validated for the three patient groups.
Results: For the no shift group, 41%, 27%, 26% and 6% of the 1420 CTs have average shifts in the range $\leqslant$2 mm, 2−5 mm, 5−10 mm and $\geqslant$10 mm, respectively. For the second group, 44%, 38%, 14% and 3.7% of the 570 samples have mean shifts in the same 4 ranges respectively. For the third group, the corresponding percentages are 54%, 32%, 13%, and 0.7% respectively. The daily setup uncertainties for these three groups as shown in table 1 demonstrate a monotonic decreasing nature of the mean shifts. Thus 15 IGRT fractions are more effective to reduce the setup variation than 10 and 5 IGRT sessions. Results and methodologies of the dynamic margin will be presented.

Table 1. Setup shifts for three patient groups

Fraction ID	No shift	One shift	Two shifts
1−5 Samples	1420	570	270
S.D. (mm)	5.92	5.95	5.78
6−10 Samples	–	570	270
S.D. (mm)	–	4.36	4.48
11−15 Samples	–	–	270
S.D. (mm)	–	–	3.38

Discussions and Conclusions: Our IGRT method employed a flexible adaptive targeting technique and can be generalized to treatment of cancers other than prostate cancer.

4027 POSTER

Results of the feasibility stage of STAMPEDE: a Multi-Arm, Multi-Stage phase II/III trial in patients with high risk prostate cancer (MRC PR08, ISRCTN78818544)

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Introduction: Most drug trials in prostate cancer (PCa) concentrate on patients with hormone refractory disease. Drugs which work in end stage disease may work better earlier in the disease. STAMPEDE tests 6 treatment approaches for patients with high-risk localised or metastatic PCa who are commencing long-term hormone therapy (HT).
Material and Methods: The trial uses Multi-Arm Multi-Stage (MAMS) methodology. There is an initial UK-based Pilot Stage of 210 patients (for feasibility and safety) followed by 4 Efficacy Stages to ~3,300 patients internationally. Patients are approached before or www.stampedetrial.org).
Results: Pilot Phase accrual was completed in 17 months and 213 patients had been recruited by 31-Mar-07. The main patient barrier to recruitment has been anxiety about chemotherapy but the accrual rate has been satisfactory. The median age is 64 years; 161, 50 & 2 patients have WHO performance status 0, 1 & 2. Of 192 newly diagnosed patients, 44 have T3/4 N0 M0 histologically confirmed adenocarcinoma with PSA > 40 ng/ml or Gleason score 8−10; 128 have N+ or M+ histologically confirmed adenocarcinoma; 20 have multiple sclerotic bone metastases with PSA > 100 ng/ml but no biopsy. An additional 21 patients have been entered having previously relapsed following local treatment & now have either PSA > 4 ng/ml with PSADT 20 ng/ml (n = 4). Safety data from the Pilot Phase will be reviewed by the trial's Independent Data Monitoring Committee in June 2007.
Conclusions: Recruitment to STAMPEDE is feasible and has been well supported by urologists & oncologists, despite the trial's apparent complexity. Patients report liking the 2 stage PIS which provides sufficient information without overload. Despite widespread PSA testing in UK, there are many newly diagnosed patients who meet the trial entry criteria.

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 $\geqslant$50% was found in 9 pts (33.3%). Median time to PSA progression was 3.2 months (95% CI 2.7−3.7 months) and median OS was 20.9 months (95% CI 14.5−27.3 months). No G3−4 hematologic or non-hematologic toxicities have been observed. Preliminary pharmacodynamic data indicate that a significant difference was observed in TSP-1 and VEGF levels between responders and non responders pts at day 84 of treatment. Indeed, the responders showed a significant increase of TSP-1 plasma concentrations (163.7$\pm$22.3% at day 84 vs. 100% at day 0; $P < 0.05$) and a concomitant significant decrease of plasma VEGF levels (29.8$\pm$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: $EFpost = 4.85 - 0.25 \times IPSS$.
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