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.