7035 POSTER

Offline position correction based on implanted markers gives in clinical practice an adequate coverage of the prostate and base of seminal vesicles, comparable to the planned dose

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Background: To determine the best position correction protocol for prostate radiotherapy using repeat CT scans and daily electronic portal imaging (EPI).
Material and Methods: We analysed 350 EPIs and 117 repeat CT scans from ten prostate cancer patients who were treated with curative intent: 77 Gy to the prostate bed and 70 Gy to the base of the seminal vesicles (SV). Before treatment, 4 gold markers were implanted in the prostate. Intensity modulated radiotherapy plans were made with an 8 mm margin. To determine the total received dose, while taking organ motion (including rotations) into account, CT scans were acquired in treatment position daily during the first week and weekly thereafter. For position verification, we performed daily EPI using orthogonal fields. From these portal images we determined the shift in bony anatomy and markers. With these data we simulated various position correction protocols: online and offline based on the position of the markers and the bony anatomy. These corrections only contained translations, because rotations cannot be corrected for. Using the original beam set-up, the dose distribution was recalculated on the repeat CT scans to determine the daily variation of the dose. From these dose distributions the accumulated dose on the prostate and the SV was determined for the different simulated position correction protocols.
Results: In case of no setup corrections, the standard deviations (SD) of the systematic displacements were 1.5 mm in left-right direction, 2.8 mm in anterior-posterior direction and 3.5 mm in the craniocaudal direction. The corresponding SD of the random displacements were 2–2.8 mm in each direction. The average D99% of the prostate over all patients is above 73.15 Gy (95% of the prescribed dose) for all protocols, even using skin alignment only. However, when looking at individual patient data, on- and offline marker based positioning gave the highest coverage of the prostate. The D99% of these cases were all above 74 Gy and within 1% of the planned dose. For the SV the D99% is for all individual patients above 66.5 Gy (95% of the prescribed dose) for the online and offline marker position correction protocol. For the other correction protocols the D99% is lower in individual patients.
Conclusion: Using repeat CT scans to include anatomical variation and the actual displacements on the linac, we found that offline position verification with gold markers aimed for adequate treatment of the prostate and base of seminal vesicles is satisfactory using an 8mm margin.

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Phase II study with pharmacodynamic evaluation of docetaxel-prednisone (DP) in combination with metronomic cyclophosphamide (CTX) and celecoxib (C) as first line treatment in castration resistant prostate cancer (CRPC)

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Background: DP has become the standard of care for CRPC, moreover, low-dose metronomic antiangiogenic CTX and C have demonstrated a significant activity in preclinical and clinical studies without relevant toxicities. Integrating MTD chemotherapy with a metronomic schedule could be of interest in advanced prostate cancer patients.
Materials and Methods: Patients (pts) with CRPC received D 60 mg/sqm iv day 1 every 3 weeks up to 12 cycles and from day 2 continuously: P 5 mg po BID, CTX 50 mg po daily and C 200 mg po BID. Primary objective was the percentage of pts free of progression at 6 months; secondary were: PSA levels decrease $\geqslant$ 50%, objective responses (RECIST), toxicities (NCI-CTC criteria) survival and pharmacodynamic evaluations.
Results: To date 34 pts have been enrolled. Main pts characteristics were: median age 72 years (52–79 years), median PS 0 (0–2), median baseline PSA level 36 ng/ml (2.5–1309 ng/ml); main sites of disease: bone 26 pts (76%), lymphnodes 9 pts (26%), liver 1 pt (3 %). Thirty-four pts were evaluable for toxicity whereas 29 for PSA response (1 pt abandoned the study due to allergic reaction after first D administration, 1 pt had measurable disease only without expressing PSA and 3 pts did not receive at least 12 weeks of treatment). Median number of D cycles delivered was 11 (1–12) and median duration of metronomic CTX plus P and C was 237 days (21–874 days). Main grade 3 side-effects were: neutropenia (2 pt; 6%), thrombocytopenia, diarrhoea, stomatitis, dyspnea, peripheral oedema and onycholysis (1 pt; 3%). One pt required C permanent discontinuation due to skin rush. Grade 4 toxicity have been observed in only 1 pt (3%) that experienced a D allergic reaction. The rate of pts free of progression at 6 months was 85%. Overall 22 pts (76%) showed a PSA decrease $\geqslant$ 50% and 26 pts (90%) showed any PSA decrease from baseline (range: 4–99% decrease). Eight pts were evaluable according to RECIST criteria: we observed 1 CR, 2 PR, 4 SD and 1 PD. The median time to PSA progression was 7.6 months (range 1–26 months).
Conclusions: DP plus metronomic CTX and C was a feasible and tolerable regimen. Preliminary activity was also interesting. The evaluation of plasma levels of thrombospondin-1 (TSP-1), VEGF, sVEGFR-2, VE-cadherin mRNA and the expression of TSP-1 and VEGF in peripheral blood mononuclear cells, as potential surrogated markers of antiangiogenic activity of the combination, is ongoing.

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Clinical, biochemical (PSA) and radiographic benefit with sunitinib as a single agent in metastatic chemoresistant and hormone-refractory prostate cancer (HRPC) patients

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Background: Sunitinib is an oral multi-target tyrosine-kinase inhibitor of VEGFR (1, 2, 3), PDGFR (α, β), RET, KIT and FLT-3. VEGFR and PDGFR have been correlated with disease progression and poor prognosis in HRPC. There is no standard therapy for HRPC previously treated with docetaxel. Preliminary results of a phase II study presented at ASCO 2008 suggested single-agent activity and PSA decline in this patient population
Methods: Patients (pts) with highly resistant and castrated HRPC patients with rising PSA were consecutively treated under a compassionate use named-patient based with sunitinib due to no other therapeutic approved options are available. All pts were propose to receive a daily dose of sunitinib 37.5 mg continuous dose with no rest. One cycle was defined as a 3-wk period. Treatment continued until disease progression, toxicity or investigator/patient decision. Pts were evaluable every 6 wks until 4th cycle and then every 12 wks. Primary endpoint was response rate by decline in PSA >50% or measurable disease. PSA was monitored every 4 weeks.
Results: 19 pts with a median age of 73 (61–81) yrs were treated between May 08 and April 09. Median PS (ECOG) was 2; Pts had received a median of 3 previous therapy lines for the hormonorefractory setting. Baseline median PSA was 280 ng/ml (range 26–2908). Gleason score was 7 in 63% and 8–10 in 32%. Pts received a median number of 4 cycles (1.3–13.3+). Disease was measurable in 63%, and 84% were evaluable by rising PSA. 1 PR (5%) was achieved by RECIST and 10 pts (52%) had SD; median PFS was 3.5 m. PSA declined > 50% in 3/19 (16%)and 26% of pts had stable PSA. At this report 9 patients remain on study and 10 are off study (9/10 due to progressive disease and 1 for toxicity). The most common adverse events were asthenia (21% G3), diarrhea (5% G3), anemia (only G1 and 2), hand-foot syndrome (16% G3) and thrombopenia (only G1 and 2). No G4 drug-related events were seen.
Conclusion: Hints of activity with sunitinib were seen in a very highly treated population of pts with refractory to docetaxel HRPC. Tolerability was acceptable. Ongoing randomized studies should confirm the sunitinib efficacy in advanced prostate cancer.

7038 POSTER

Oral vinorelbine as a fixed-weekly schedule in taxanes-refractory advanced HRPC. A single institution experience

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Background: Vinorelbine (VRL) has been shown to be active in hormone-refractory prostate cancer (HRPC). Oral formulation of VRL represents a significant advance in the treatment of advanced cancer. The recommended doses are 60–80 mg/m^2(d1–8 q3wks). We evaluated

efficacy and toxicity of different VRL schedule administered as a fixed-weekly dose of 60 mg/m^2. The purpose of this study was to evaluate the toxicity profile and efficacy of this schedule in terms of PSA response, objective response and clinical benefit (CB) response.
Methods: Pts characteristics were: PS 0−2, adequate bone marrow, liver and renal functions. Oral VRL was adminestered at weekly dose of 60 mg/m^2 until disease progression/intolerable toxicity. PSA response was defined as a >50% fall in PSA from baseline, confirmed by a second PSA value 4 or > weeks later. Pts with measurable soft tissue disease met traditional guidelines for tumour responses. Progression was defined by objective disease progression or PSA increase of >50% above nadir or >25% above baseline. Pts were monitored clinically and with serial PSA measurements every 1 week.
Results: Thirty seven pts with progressive HR metastatic prostate cancer were evaluated. Mean (range) age was 67 years (50−88), median PSA level was 90 ng/ml(1− 4314), and median Gleason score was 7 (6−9). 23 (62%) pts had previous taxane chemotherapy and 14 pts (38%) were chemo-naive. Pts received a mean of 5.5 cycles (1cycle = 3wks) (range:1−24). Median follow-up was 12 months. Thirty three of 37 Pts (97%) achieved a decline in serum PSA. CB response was achieved in 15 out of 37 pts(40%). The PSA response was observed in 13 pts (35%). Objective response was not observed and only 6 pts showed SD (16%). The relative dose-intensity was 94%. There were no reported grade 3−4 toxicities. Only 1 treatment discontinuation was observed (esopahgitis g2). Toxicities consisted primarily of g2 anemia (25%) and mild nausea (32%).
Conclusions: Oral Vinorelbine administered as a fixed-weekly schedule of 60 mg/m^2 is a safe regimen in pts with advanced HRPC. This regimen of oral vinorelbine is an effective and well-tolerated treatment in this setting, despite a major dose-intensity administered. Further studies will be evaluated in chemo-naive and/or elderly population.

7039 POSTER

MRI based dose escalation in patients treated with salvage radiotherapy after radical prostatectomy for prostate cancer

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Purpose: We evaluated the treatment results and morbidities in patients treated with selective dose according to existence of recurrent lesions in MRI for salvage radiotherapy (RT) after radical prostatectomy (RP) of prostate cancer.
Materials and Methods: Between 2000 and 2006, 50 patients underwent salvage RT alone for PSA failure after RP. Before salvage RT, all patients were examined with MRI prospectively. Radiotherapy was done with 3D-CRT confined to the prostate bed. Irradiated dose was 66 Gy in patients without suspected gross tumor (low-dose group) or 70 Gy in patients with suspected gross tumor in MRI (high-dose group) with daily 2.0 Gy. Biochemical failure after salvage RT defined as a serum PSA value > 0.2 ng/ml above the post-RT PSA nadir. The toxicity was evaluated by Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.
Results: Median follow-up was 34 months (range: 21−99 months). Seventeen patients (34 %) experienced PSA failure and 3 (6 %) patients developed distant metastases during follow-up. The 3-year and 5-year PSA failure free survival rate was 67.1 % and 55.9% respectively. According to irradiated dose, 3-year PSA failure free survival rate was high in high-dose group, compared with low-dose group, but not significant (68.9 %:64.9 %, $p = 0.70$). The only affecting factor for PSA failure after salvage RT was pre-RT PSA level. PSA failure rate was significantly high in pre-RT PSA >1 ng/ml compared with pre-RT PSA $\leqslant$1 ng/ml (58 %:26 %, $p = 0.041$). In multivariate analysis, pre-RT PSA level was the only significant prognostic factor affecting for PSA failure rate ($p = 0.025$). During follow-up, four patients (8%) developed grade 2 toxicities that included 3 patients of incontinence and 1 patient of hematuria. There was no grade 3 or greater treatment-related toxicities.
Conclusions: In this study, high-dose group (suspected gross tumour) showed similar PSA failure free survival rate, compared with low-dose group (no suspected gross tumour). MRI evaluation before salvage RT might be useful to evaluate the disease status and to determine irradiated dose. However, the optimal dose according to disease status after PSA failure is still controversial. Further studies are needed to determine optimal irradiated dose for salvage RT in patients treated with RP according to the disease status and the benefit of combined treatment with hormonal therapy in patients with pre-RT PSA level above >1 ng/ml.

7040 POSTER

Honokiol, a natural plant product from magnolia tree, inhibits the bone metastatic growth of human prostate cancer cells

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Background: Honokiol, a soluble nontoxic natural product derived from Magnolia spp., was reported to induce apoptosis in caner cells. In this study, we investigated the effect of honokiol and the combined with docetaxel on prostate cancer (PCa) growth and its bone metastasis in experimental models.
Materials and Methods: We investigated in vitro proapoptotic effects of honokiol on human androgen-dependent and -independent PCa, bone marrow, bone marrow-derived endothelial, and prostate stroma cells. Honokiol-induced activation of caspases was evaluated by FACS analysis and Western blot. Mice bone was inoculated in vivo with androgen-independent PCa, C4−2 cells and the effects of honokiol and/or docetaxel on PCa growth in bone were evaluated. Daily honokiol (100 mg/kg) and/or weekly docetaxel (5 mg/kg) were injected intraperitoneally for 6 weeks. PCa growth in mouse bone was evaluated by radiography, serum prostate-specific antigen (PSA), and tissue immunohistochemistry regarding the markers of cell proliferation, apoptosis, and angiogenesis.
Results: Honokiol inhibited cell growth through the induction of apoptosis in all cell lines tested. In PCa cells honokiol-induced apoptosis was via the activation of caspases 3, 8, and 9, and the cleavage of poly-adenosine diphosphate ribose polymerase in a dose- and time-dependent manner. Honokiol was shown to inhibit the growth and depress serum PSA in mice harboring C4−2 xenografts in the bone and the combination with docetaxel showed additive effects that inhibited further growth without evidence of systemic toxicity. Immunohistochemical staining confirmed honokiol exhibited growth-inhibitory, apoptotic, and antiangiogenic effects on PCa xenografts.
Conclusions: The combined therapy of honokiol and low-dose docetaxel may improve patients' outcome in androgen-independent prostate cancer with bone metastasis.

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Active potential of sonic Hedgehog signaling between human prostate cancer cells and normal/benign but not cancer-associated human prostate stromal cells

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Backgrounds: Sonic hedgehog (Shh) signaling is known to affect normal prostate development and possibly mediate prostate cancer-stromal interaction. We investigated Shh signaling between human prostate cancer cells and prostate stromal cells isolated from normal/benign and malignant tissues and determined the downstream *stromal targets* of this interaction.
Materials and Methods: Shh and its downstream target transcription factor, Gli1 mRNAs was assessed by RT-PCR in prostate stromal cells established from normal/benign (NPF), cancer-associated areas (CPF), or human bone marrow stromal (HS27A) cells in cell culture containing recombinant Shh. Co-culture and conditioned medium (CM) studies were also conducted to determine the effects of Shh on C4−2 cell growth using C4−2-Luc cells stably transfected with Luciferase gene, in the presence or absence of cyclopamine, Shh-Gli1 signaling inhibitor. The Results were confirmed by *in vivo* studies in chimeric subcutaneous prostate tumors comprised of C4−2-Luc and NPF.
Results: Recombinant Shh induced Gli1 expression in cultured NPF but not CPF, HS27A or C4−2 as evaluated by RT-PCR. Shh stimulated C4−2-Luc growth when co-cultured with NPF but not CPF nor HS27A, and this effect was completely abrogated by cyclopamine. We have also shown that osteonectin (ON) expression is induced by Shh in stromal cell. Although C4−2 cells expressed Shh and its expression level was not affected by exogenous added Shh, the CM of C4−2 induced growth of NPF, not CPF, and this induction was completely blocked by cyclopamine. A chimeric tumor of C4−2 and NPF demonstrated to respond to cyclopamine