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.

7041 POSTER

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

which inhibited the expression of androgen receptor (AR), prostate specific antigen (PSA), and Gli 1, and induced apoptosis (M30); cyclopamine was found to inhibit serum PSA in mice harboring chimeric prostate tumours of C4−2 and NPF. Because co-culture of C4−2 and NPF maintained the expressions of Shh and Gli 1 in prostate cancer epithelium. These results suggest prostate cancer cells stimulated the growth of normal/benign but not cancerous prostate stromal cells through Shh-mediated stromal target genes.
Conclusions: A chimeric C4−2 and NPF model was established to assess the role of Shh signaling in human prostate cancer. Shh induced Gli1 target gene expression in normal/benign but not cancerous prostate stromal or bone stromal cells, which confer increased prostate cancer cell growth. A "vicious cycle" mechanism could result from aberrant Shh-Gli1 signaling between prostate cancer and normal/benign stromal cells.

7042 POSTER

Correspondence between Common Terminology Criteria for Adverse Events v3.0 and four self-report toxicity questionnaires during and after radiotherapy for prostate cancer

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Background: Accurate measurement of side effects of radiotherapy for prostate cancer is important in the development of a more effective treatment. The Common Terminology Criteria for Adverse Events v3.0 (CTCae v3.0) is a standardized scoring system, used for assessing side effects in patients during or after treatment for cancer. Currently no self-report questionnaires, specifically developed to monitor side effects of radiotherapy, such as cystitis and proctitis, are validated. Therefore the aim of this study was to evaluate the correspondence between the CTC and four self-report questionnaires during radiotherapy for prostate cancer.
Methods: 30 patients completed three or four self-report questionnaires, the International index of Erectile Function (IIEF), International Prostate Symptom Score (IPSS), Radiation-Proctitis questionnaire (RPQ) and the Radiation-Cystitis questionnaire (RCQ). IPSS and IIEF have already been validated in urology. The latter two are in house developed questionnaires, based on EORTC questionnaires. A student and a physician independently assessed a CTC. All separate items of the questionnaires were linked to specific CTC scores. The data were introduced in statistical software program SPSS to find a correlation, between the standardized CTC and the questionnaires specialized for prostate cancer, using the Spearman method (CC). Kappa (κ) and the raw agreement were used to estimate the inter-observer variability.
Results: Only CTC items regarding hemorrhage GI and GU and incontinence for urine correlated significantly with the corresponding questions of the RPQ and the RCQ. The inter observer agreement was high ($\kappa > 0.5$) for the same items. Only the IPSS item regarding nocturia showed a significant correlation with the matching CTC item. Remaining matching items showed low correlations. The IPSS and corresponding questions from the RCQ had high CCs. The raw agreement was >0.5 except for CTC Ejaculatory dysfunction, where it was 0.41.
Conclusion: Grading with CTC does not allow for accurate scoring of side effects. To overcome this problem self reported questionnaires can be used. Clear guidelines should be made on how to convert data to a CTC grade, to limit inter-observer variability. Questionnaires should be incorporated into daily practice to gather more information on treatment related side-effects.

7043 POSTER

Prediction of biochemical recurrence after radiotherapy treatment for prostate cancer: does PSA response during treatment matter?

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Background: The incidence of prostate cancer is rising in the Western world. Monitoring of total PSA levels, possibly combined with free/total PSA (f/t) ratio, yields valuable information for diagnosis and recurrence after treatment. The goal of the current study was to estimate whether changes in PSA levels during radiotherapy treatment are predictive of the probability of biochemical recurrence during follow up.
Materials and Methods: PSA levels were determined weekly during and at least every three months after radiotherapy treatment for 91 prostate cancer patients (mean age 71.7; sd 5.9 years). All patients were treated with EBRT to a total dose of 68 Gy. Median follow up after treatment was 55 months (range 9−93). Biochemical recurrence was defined as at least two measurements of total PSA level of nadir plus 2 ng/ml or as a start of hormonal treatment. Of all patients, 35 experienced a biochemical failure. Possible predictors of recurrence during radiotherapy treatment were (for both total PSA and f/t ratio) minimum levels, maximum levels, maximum decrease from baseline, maximum increase from baseline and average difference from baseline. The predictors were first studied in univariate logistic regression analyses. Significant predictors were then corrected for age and tumor T stage (N and M stage was 0 in all patients) in multivariate logistic regression analyses after which predictive value of the model was assessed using area under the ROC curve (AUC).
Results: Both minimum total PSA level and maximum f/t ratio were significant predictors from the univariate logistic regression analyses (p respectively 0.04 and 0.025). Both remained significant when corrected for age and T stage. AUC for both models was 0.69 and 0.64 respectively (p respectively 0.003 and 0.024).
Conclusions: Measurement of total PSA levels and f/t ratio during radiotherapy treatment can be predictive of biochemical recurrence afterwards. This applies specifically to the minimum total PSA level and to the maximum f/t ratio. The latter is not surprising since the f/t ratio increases if total PSA levels decrease. There is still room for improvement of the prediction of biochemical recurrence, which should be the subject of a more extensive clinical study incorporating clinical data, blood values apart from PSA and imaging data.

7044 POSTER

Pharmacokinetic analysis of two dosing schedules of the angiokinase inhibitor BIBF 1120 in patients with hormone-refractory prostate cancer who progressed after docetaxel treatment

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Background: BIBF 1120 (Vargatef™*) is a novel, oral, potent angiokinase inhibitor blocking the vascular endothelial growth factor receptor 1/2/3, fibroblast growth factor receptor 1/3, and platelet-derived growth factor receptor α/β tyrosine kinases at nanomolar concentrations. This randomized, open-label, multicenter Phase II study evaluated the efficacy, safety and pharmacokinetics (PK) of two doses of BIBF 1120 in patients with metastatic hormone refractory prostate cancer (HRPC) that had progressed after docetaxel therapy.
Methods: Patients were randomly assigned and treated with BIBF 1120 until disease progression or dose-limiting toxicity. The primary endpoint was response rate defined as a confirmed decline of prostate-specific antigen by $\geqslant$20%. PK analysis was performed for PK samples of 36 patients. PK sampling occurred on Days 1 and 29, and every 2 weeks thereafter. Trough plasma concentrations were taken 8−14 hours after dosing. The distribution of BIBF 1120 plasma concentrations was described using graphs and descriptive statistics.
Results: 81 patients were randomly assigned to receive either 250 mg bid (n = 41) or 150 mg bid (n = 40) of BIBF 1120 as monotherapy. On Day 1, BIBF 1120 plasma con-cen-trations increased within the first 3 hours after dosing in the 150 mg bid and 250 mg bid groups; maximum values were 66.3 ng/mL and 124 ng/mL, respectively. On Day 29, maximum plasma concentrations were 54.9 ng/mL and 112 ng/mL in the 150 mg bid and 250 mg bid groups, respectively. BIBF 1120 plasma levels had reached steady state by Day 29 in both groups; this may have occurred earlier but there was no PK sampling between Days 1 and 29. Overall, pre-dose plasma concentrations remained stable over the 155-day observation period in both groups; interpatient variability was moderate to high. No systematic change in trough plasma concentrations or deviation from dose propor-tio-nality of BIBF 1120 was observed in either group. The gMean pre-dose plasma con-centrations of BIBF 1120 were higher in the 250 mg bid group compared with the 150 mg bid group.
Conclusions: For both dose groups, BIBF 1120 pre-dose concentrations did not deviate from dose-linearity in this study. For both dose groups, pre-dose concentrations remained stable over the treatment period.
*Trade name not FDA approved