4 cycles. Docetaxel was given at a dose of 75 mg/m2 upon completion of each antisense infusion. Adverse reactions were assessed using the CTC criteria version 2.

Results: Ten patients were registered; 9 were treated, receiving a median of 2 cycles (range 0-4). Four pts were treated at the 5 and 7 mg/kg/day dose levels of G3139 and 1 pt received 9 mg/kg/day. Grade 4 adverse events were: 1 pt who experienced a myocardial infarction unrelated to treatment, and 5 pts who developed neutropenia. Grade 3 events possibly related to treatment were hyperglycemia (2 pts), leukopenia (4 pts), and hypophosphatemia (2 pts). Six pts are evaluable for response, 4 of whom had stable disease after 4 cycles; 2 pts progressed after 2 cycles.

Conclusions: The combination of G3139 and docetaxel is well-tolerated. The maximum tolerated dose has not yet been reached using G3139 at 9 mg/kg/day and docetaxel at 75 mg/m2. Further study of the combination is planned to better define efficacy.

802 POSTER

Association of polymorphisms at the prostate-specific antigen gene and blood circulating epithelial prostate cells

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Purpose: The prostate-specific antigen (PSA) gene is under regulation by steroid hormones. The PSA gene has a polymorphic ARE sequence with two alleles, A and G. The detection in blood of specific prostatic cells messenger RNAs has been suggested as a method of search for the presence of blood circulating prostatic cells. We hypothesize that these genetic polymorphisms at PSA gene may influence the presence of circulating prostate epithelial cells in the peripheral blood of prostate cancer patients.

Methods: In the present study we assayed PSA ARE1 genotypes and a highly sensitive reverse transcription PCR assay was used to detect the presence of mRNAs from PSA and PSM (prostate specific membrane antigen) in the blood of 61 patients.

Results: We found PSA AA genotype in 31.5% (6/19) of the PSM mRNA positive and in 52.3% (22/42) of the PSM mRNA negative cases. Regarding PSA mRNA positive cases we found that 85.6% (6/7) present the PSA AA genotype and in PSA mRNA negative cases only 38.8% (21/54) present the PSA AA genotype. This difference was statistically significant (p=0.018).

Conclusion: These results indicate that polymorphism in the PSA gene promoter influences the presence of PSA mRNA positive blood circulating epithelial cells and that may help to understand the biological mechanisms of metastization in prostate cancer.

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803 POSTER

A randomized phase II study comparing tolerance and efficacy of goserelin ('Zoladex') alone or combined with raltitrexed ('Tomudex'), in high-risk advanced prostate cancer (PCa): preliminary results on tolerance

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Introduction: So far chemotherapy has been mostly evaluated in end-stage androgen-independent PCa where it has limited efficacy. Since PCa often contain a primarily sub-population of androgen-insensitive cells, it is reasonable to expect that early application of chemotherapy will delay the onset of hormone-independence. The objective of this randomized, prospective Phase II study was to compare tolerance and efficacy or a treatment with goserelin acetate ('Zoladex') alone or combined with raltitrexed ('Tomudex') in patients with high-risk PCa.

Material & Methods: 25 patients were enrolled in the study between 01/1999 and 06/2000. Patients were aged 70 years or less with histologically confirmed PCa (Gleason score ~8 for those aged > 55 years) and had N+ or M+ disease at diagnosis. Patients with biochemical failure were included if PSA doubling time was <10 months and recurrence occur within 12 months after radical prostatectomy with or without radiotherapy. Patients received goserelin acetate (10.8 mg sc depot every 12 weeks) alone or combined with raltitrexed (3 mg/m* iv every 21 days for 6 months). Toxicity was monitored using NCI common toxicity criteria evaluation.

Results: Of the 25 patients were enrolled in this study, 18 receiving the combination regimen. A total of 85 cycles of raltitrexed were administered. Grade 1 and 2 endocrine toxicity (hot flushes) was recorded in a total of 19 patients from boths groups. In the goserelin/raltitrexed group, 19 grade 1or 2 adverse events were reported in 14 patients: grade 2 fever (in the absence of neutropenia, defined as absolute granulocyte count <1.0 x 109/L) in 12 patients; reversible grade 2 liver toxicity in 2 patients, grade 2 endocrine toxicity (hypoglycemia) in 2 diabetic patient, grade 1 neutropenia in 10 patients. Complete response as defined by a normalisation of the PSA was observed in 4 patients from the gosereline group and in 17 from the gosereline/raltitrexed group. Two patients had dose reduction for a decrease renal function

Conclusions: These preliminary results indicate that the combination of goserelin acetate and raltitrexed is safe and well tolerated in patients with high-risk PCa. Whether or not the combination results in a clinical benefit to patients will require longer follow-up. 'Tomudex' and 'Zoladex' are trade marks, the property of Zeneca Ltd (part of AstraZeneca).

804 POSTER

The efficacy of endocrine combination therapy with aminoglutethimide and hydrocortisone in metastatic prostatic cancer refractory to standard endocrine therapies

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Metastatic prostate cancer, progressive after first- or second-line anti-androgen treatment is considered hormone-resistant and remaining treatment options are limited. The adrenal gland is an important source of androgens and after conversion by aromatase indirectly of estrogens. Adrenalectomy has been used as second-line endocrine therapy. Evaluation of treatment efficacy was hampered by absence of evaluable tumour parameters. Presently, PSA is accepted as an adequate surrogate marker for response evaluation. In a prospective phase II study we investigated the combination of the aromatase inhibitor aminoglutethimide 1000 mg/day and hydrocortisone 40 mg/day in 35 patients (pts) with metastatic prostatic cancer resistant to first-or second-line endocrine therapy. Biochemical (change in PSA) and subjective response were used as main determinants for response evaluation. In addition, if evaluable lesions were present, objective assessment was done by CT scan and X-ray investigations. Main patient characteristics were median age: 67 years; median WHO performance status: 1; sites of metastases, bone: 94%, lymphnode: 17% and lung: 3%. PSA was measured every month. In 3 pts (9%) the PSA value normalised and in 10 pts (29%) a decline in serum levels of at least 50% occurred (CR + PR: 37%). Moreover, 17 pts (49%) remained stable (total benefit 86%). Median time to progression in responding and all pts were 9.5 and 5 months, respectively (range 0.5-23.5 months). Median survival for these groups was 23 and 14.5 months, respectively. Of 7 pts with measurable disease 2 showed a PR and 5 stable disease. Improvement in general condition, pain, feeling of well being was noted in two-thirds of pts. Therapy was well tolerated with only 8 adverse event episodes, mostly grade I/II and 2 cases of grade III skin toxicity. In conclusion, aminoglutethimide in combination with hydrocortisone is a valuable active and tolerable second-or third-line palliative therapy for pts with hormone-resistant prostatic cancer.

805 POSTER

Optimal brachytherapy for prostate cancer: LDR vs HDR - the view from radiobiological models, or "you take the high road and i'll take the low road"

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Purpose: Clinical evidence points to superior outcome with dose-escalation and suggests that brachytherapy may achieve superior dose-escalation when compared with external-beam for localized prostate cancer.

Methods & Materials: An algorithm based on the LQ model is constructed for fractionated and protracted irradiation. It includes tumor cell-line derived LQ parameters, repopulation, repair kinetics and isotope decay. Dose inhomogeneities for LDR (I-125 and Pd-103) and HDR (Ir-192) from patient-derived DVH are incorporated. Three risk groups are defined in terms of radiobiological parameters to correspond to clinical risk: Favorable - iPSA<10, bGS<7 and stage T2, Intermediate - one factor increased, and Unfavorable - two factors increased. Tumor control probabilities (TCP) are predicted for LDR monotherapy and for LDR and HDR boost after 45Gy EBRT. Several HDR regimens are considered.

Results: LDR brachytherapy is less susceptible to uncertainties in alpha/beta than EBRT or HDR, and more susceptible to repopulation. Model TCP for each regimen and risk group are compared with clinical series (Table 1). Dependence upon biologic assumptions will be discussed.

Table 1

	Favorable	Intermediate	Unfavorable
Model TCP (%)			
EBRT 69Gy	80	50	20
I-125 mono	92	95	35
Pd-103 mono	79	96	84
EBRT+I-125	99	99	80
EBRT+Pd-103	99	99	97
EBRT+Ir-192	98	94	56
Clinical Series			
MSKCC 68Gy	83	52	19
MSKCC 78Gy	94	77	51
Blasko I/Pd	94	84	54
Blasko EB+I/Pd	87	85	62
Eulau EB+Ir	96	72	49

Conclusions: 1) LDR brachytherapy as monotherapy predicts superior tumor control as compared with EBRT to conventional doses and equivalent to escalated doses, 2) both LDR and HDR in combination with EBRT predict superior tumor control when compared with either modality alone, 3) for Favorable cancers both LDR and HDR predict equivalent tumor control, however 4) for Intermediate and Unfavorable cancers, LDR predicts superior tumor control compared with HDR. These model results are supported by long-term clinical outcomes and suggest potentially improved dose-escalation with LDR brachytherapy.

806 POSTER

CT/MRI image fusion based postplans significantly improve the quality control after prostate seed brachytherapy

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Introduction: Brachytherapy using seeds has become a standard treatment for localized prostate cancer in the U.S. and is becoming more popular in Europe. In order to provide a good service for the patients a rigid quality control scheme is imperative. Studies have shown that the D90 is the only predictive parameter when calculating a postplan. The D90 is highly dependable on the size of the prostate outlined on the postplan. In most cases a CT is being used to perform this plan. Delineating the contours of the prostate on a CT usually leads to an overestimation of the prostate size thus leading to an inaccuracy in the dosimetry.

Material and Methods: In a multicentre cooperation 35 consecutive patients treated were evaluated comparing CT and TRUS images taken immedeately after the implant as well as CT/MRI image fusion. The prostate contours were outlined by experienced radio-oncologists. 3-D calculations were performed using the VariSeed 6.7 software. The image-fusion protocol required the following steps: CT scan of the prostate after seed implantation, MR scan thereafter in the same position, fusion of the two image sets with a dedicated sofware, transfer of the new image set to the VariSeed, definition of target and organs at risk in the fused images set and calculation of the definitive dosimetry. The accuracy of image fusion was quantified by recording the distance between the center of the prostatic urethra on axial MR vs. CT images after fusion in each patient.

Results: The average distance between the center of the prostatic urethra on axial MR vs. CT scan was 1mm (range, 0mm-4mm) proving a high accuracy of the co-registration. The median prostate TRUS volume was 32cc. The median prostate CT volume was 34% greater (43cc). The median prostate on CT-MRI was 34cc (2,5% greater). The D90 (150 Gy vs. 156 Gy) and V100 (82% vs. 88%) were significantly different between CT and CT/MRI postplans (p value 0.003).

Conclusion: CT based postplan is widely used in prostate brachytherapy yet it proved to be inaccurate. CT-MRI images predict the prostate size with a high degree of accuracy improving significantly the quality of the dosimetry and DVH related parameters providing a more consistent way of assessing prostate seed implants. CT/MRI image fusion is very costly and time consuming, a special software is required to fuse the images. Further efforts should be made to improve TRUS based postplanning in order to accurately produce postplans at low cost.

807 POSTER

Conformal radiation therapy of 180 patients with prostate cancer: Risk of biochemical failure

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Purpose: Analysis of factors influencing biochemical failure after 3-D conformal radiation therapy of prostate cancer to a total dose of 66 to 70 Gy.

Materials and methods: 180 patients with a median follow up of 30.5 months (12±67 months) were retrospectively analysed. T-Stage: T1 19%, T2 56%, T3 24%, T4 1%. Grading: G1 17%, G2 70%, G3 13%. Pretreatment PSA: Median 11.6 ng/ml (0.8-100 ng/dl). Dose to the prostate: Median 70 Gy (59.4-70.2 Gy). Neoadjuvant hormonal therapy: 72% of the patients, radiation alone: 28%. Biochemical failure was defined according to the ASTRO consensus criteria (three consecutive increases in PSA). The influence of the following factors on biochemical failure were studied in uni- and multivariate analysis: Age, body-mass-index, T-stage, grading, Gleason score, pretreatment PSA, neoadjuvant hormonal therapy, prostate dose, PSA nadir and time to nadir.

Results: Biochemical-failure-free-survival after 3 years (bNED-3-YS) was 75% (Kaplan/Meier). The following factors had an influence on biochemical failure (Kaplan/Meier) in univariat analysis: Age: <72 vs. > 72 years (bNED-3-YS: 69% vs. 80%, p=0.03), T-stage: T1+T2 vs. T3+T4 (bNED-3-YS: 80% vs. 60%, p=0.04), grading: (bNED-3-YS: G1 89%, G2 76%, G3 46%, p=0.02), pretreatment PSA <20 vs. >20 ng/dl (bNED-3-YS: 84% vs. 49%, p<0.001), PSA nadir <0,5 vs. >0,5 ng/ml (bNED-3-YS: 84% vs. 55%, p=0.001), time to nadir <12 vs. >12 months (bNED-3-YS: 82% vs. 70%, p=0.055). Independent prognostic factors in multivariate analysis were: pretreatment PSA, grading, height of nadir and age.

Conclusion: PSA before therapy, tumour grading, height of the PSA nadir and age are valuable criteria to estimate the risk of biochemical failure after conformal radiation therapy of prostate cancer, which is in concordance with other investigators.

808 POSTER

The selective endothelin-a receptor antagonist improves quality of life (QOL) weighted time to progression in hormone refractory prostate cancer patients

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Atrasentan, a selective endothelin-A receptor antagonist, has recently demonstrated a significant delay in time to clinical progression of disease in a study of HRPCa patients (Placebo=129 days, 10 mg Atrasentan = 196 days, p=0.02, 52% delay). In this study atrasentan was well tolerated. Clinical progression (defined as the onset of opiate treatment for disease related pain or new disease-related events requiring intervention) resulted in a decline in all patients' QoL by 20%, as measured by EORTC Global score. Conventional analyses of time to progression do not account for treatment effects on patients' perception of their health status. Therefore, to assess the cumulative effects of atrasentan on patients' health status the area under the curve for QoL-weighted time to progression (AUC) was compared across treatment groups, with the assumption of an equal length of follow-up, over the one-year course of follow-up. EORTC QLQ-C-30 and FACT-P instruments were used to evaluate health related QoL of HRPCa patients randomized to oral atrasentan, 2.5 mg (N=95) or 10 mg (N=89), or matching placebo (N=104) once daily. For 10 mg atrasentan patients the AUCs for EORTC physical, social, and emotional functioning were significantly better than those of the placebo group (p<0.05). Their AUC responses for pain and appetite loss were also significantly better than placebo (p<0.05). The AUCs for EORTC global, role and cognitive functioning, fatigue, nausea and diarrhea and overall FACT-P domains demonstrated strong trends benefiting10 mg atrasentan patients over placebo (p<0.10). For the remaining EORTC domains (constipation, dyspnea and sleep disturbance) the AUCs were statistically indifferentiable across treatment groups. Additionally, there were no statistical differences between the 2.5 mg and 10 mg atrasentan group responses across all QoL domains. Our AUC analysis demonstrates that HRPCa patients treated with atrasentan experience a significantly longer time to disease progression after adjusting for the perceptions of their health status.