PSA will be achieved at higher dose levels is not known. However, the modest effect on PSA observed to date suggests some biologic activity. Once MTD is reached, phase II trials of CV787 alone and in combination are planned.

798 POSTER

Baseline quality of life measured with the EORTC QLQ-C30 helps to select a subset of 'good prognosis' metastatic hormone refractory prostate cancer patients

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Introduction and Objectives: Patients with metastatic hormone refractory prostate cancer (HRPC) are often viewed as an homogeneous group with median overall survival lasting about one year. Few prognostic factors have been identified so far. Quality of life (QL) measurements have rarely been considered as potential prognostic factors in this disease. Using data from 494 metastatic HRPC patients randomized in three EORTC trials (30903, 30921, 30944), we attempted to form three prognostic groups using clinical and biochemical parameters together with the results from baseline QL assessment.

Material and Methods: The 15 scales from the EORTC QLQ-C 30 (version 1.0) and ten baseline clinical and biochemical variables were considered. Univariate and multivariate Cox proportional hazard models stratified for trial and treatment were used. The 0.01 statistical significance level was used.

Results: Insomnia, dyspnoea and appetite loss, age, bone scan result, performance status (WHO PS) and hemoglobin level were independent predictors of survival in the multivariate analysis. Based on these 7 factors, a prognostic index was computed: PI=0 2 (if dyspnoea 67-100) 1 (if insomnia 33) 2 (if insomnia 67-100) 1 (if appetite loss 33) 2 (if appetite loss 67-100) 1 (if age 66-75) 2 (if age >75) 1 (if 5-15 hot spots) 2 (if >15/superscan) 2 (if WHO PS >1) 2 (if Hemoglobin WHO grade >0). The patients could then be classified into three groups: good prognosis (PI 0-3: 29%) with 18.7 months median survival, intermediate prognosis (PI 4-6: 39%) with 11.9 months median survival and poor prognosis (PI >6: 32%) with a median survival of 6.0 months.

Conclusion: QL dimensions of insomnia, dyspnoea and appetite loss add independent prognostic information over clinical and biochemical factors such as age, performance status, hemoglobin and bone scan results for predicting the survival of HRPC patients. They enable the definition of three groups of HRPC patients with median duration of survival from 6.0 months (poor prognosis) to 18.7 months (good prognosis). Twenty-nine percent of the patients fall in the 'good prognosis' group.

799 POSTER

Androgen suppression of advanced prostate cancer: intermittent or continuous therapy?

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Purpose: In up to 80% of advanced prostate cancer patients, the condition is improved by endocrine androgen ablative therapy. However, over time androgen independence occurs, leading to progression of the cancer. In the last few years a new therapeutic concept of hormonal treatment has emerged based on the observation that when androgen-dependent Shionogi Carcinoma in mice are intermittently exposed to androgen withdrawal, apoptotic regression of the tumour is induced. While continuous androgen suppression (CAS) can lead to a loss of libido and sexual function, intermittent androgen suppression (IAS) may improve the quality of life of patients in the intervals between hormone treatments. Data from pilot studies suggest that the cyclical effects of such treatment modality could be monitored by measuring prostate specific antigen (PSA) concentration. To obtain more data on IAS an international, prospective, randomised clinical trial was initiated in 1998. The primary objective of this study was evaluation of time to clinical tumour progression and/or PSA escape (defined as PSA concentrations over 50 ng/ml). The major secondary objective was evaluation of patients' quality of life.

Methods: Proven advanced prostate cancer patients showing normalisation of PSA (below 4 ng/ml) after 6 months of maximal androgen blockade using the combination of buserelin depot and nilutamide, became eligible for randomisation to either IAS or CAS. In total 193 patients have been randomised, 155 classified as T2-4NxM1 and 38 classified as T2-4N1-3M0. The first patient was entered in March 1998 and the follow-up of all patients enrolled ends in August 2001.

Results: Interim analyses suggest that the patients enrolled are performing well. On average, patients randomised to intermittent therapy had to restart therapy at month 14. The safety profile evaluated to date demonstrated good tolerability. At time of analysis, a total of 66 patients were withdrawn, 25 patients in the IAS group, 41 patients in the CAS group. Reasons for withdrawal were mainly clinical progression; other reasons were patient's wish or death from prostate cancer or another cause.

Conclusion: This international, prospective, randomised trial suggests that IAS is a feasible alternative to CAS.

800 POSTER

A designer inhibitor of a novel protein-kinase causes regression of human hormone refractory prostate cancer xenografts in nude mice

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A Src-related kinase, previously considered to be restricted to hemapoietic cells, was found to be expressed in the normal prostate gland. Moreover, its level is markedly elevated in prostate cancer, as determined by immmunohistochemistry and in-situ hybridization utilizing a probe specific to that kinase. The prostate gland in knockout mice for that kinase, resembled the morphology found in castrated animals. Therefore we set out to test a designer compound, directed against this kinase, for the treatment of Hormone Refractory Prostate Cancer (HRPC).

Our comparative analysis of the kinase domain revealed a distinct structural motif allegedly involved in substrate-binding. Short peptides (7 aa) derived from this region specifically inhibit substrate-phosphorylation by that kinase and abrogate the proliferation of HRPC cells (PC3 and DU-145) in-vitro at sub-micromolar range. Following structural optimization, a lead compound, KRX-123, was formulated for i.v. injection and tested for its in-vivo efficacy against established DU-145 tumors in nude mice (around 400 sq.mm at the initiation of treatment).

Once a week injection of 2.5 to 10 mg/kg of KRX-123 caused complete inhibition of tumor growth within a month, while in the control group, the tumor doubled in size during the same period of time (n=6 in each group). In the high-dose group, approximately two-third of treated animals had non-palpable remnant, by week 12. Pre-Clinical studies in rats and dogs showed that KRX-123 is non-toxic at that concentration range.

In conclusion, a promising drug candidate has been discovered for prostate cancer. A phase I/II clinical trial, testing KRX-123 in patients suffering from HRPC, is scheduled to begin in 2001.

801 POSTER

BCL-2 antisense (G3139) plus docetaxel for treatment of progressive androgen-independent prostate cancer

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Purpose: G3139 (Genta, Inc., Berkeley Heights, NJ) is an 18 mer phosphorothioate antisense oligonucleotide that targets the mRNA of BCL2, which encodes an antiapoptotic protein that is expressed in androgen-independent prostate cancer. BCL2 has also been implicated in resistence to treatment. Preclinical data have shown that G3139 has synergistic antitumor effects when used in combination with docetaxel (Taxotere®, Aventis Pharmaceuticals, Parsippany, NJ) in xenograft models. The purpose of this trial was to define the dose of G3139 with docetaxel for the treatment of patients with progressive androgen-independent prostate cancer.

Methods: Patients (pts) were treated with escalating doses of G3139 of 5, 7, and 9 mg/kg/day in cohorts of 3-6. G3139 was delivered as a five-day continuous intravenous infusion, every 3 weeks, for a maximum of

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.