Bladder and prostate cancer

113 ORAL

A pathogenetic role for prostate-specific antigen (PSA) in osteoblastic bone metastasis: Implications for drug treatment of hormone-resistant disease

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Purpose: Prostate cancer metastatic to bone typically presents with sclerotic lesions, whereas bone metastases of non-prostatic origin are more often lytic. We sought to establish whether intralesional growth factor bioavailability correlates with the osteoblastic phenotype.

Methods: Marrow reamings from patients with osteoblastic (prostate cancer) or osteolytic (breast cancer) bone metastases were assayed for expression of growth factors and the insulin-like growth factor-1 (IGF-1) extracellular binding protein, IGF-binding protein-3 (IGFBP-3). LNCaP cells expressing the serine protease PSA were used for in vitro studies.

Results: Growth factor levels are indistinguishable in sclerotic and lytic metastases. In contrast, PSA varies directly with the degree of sclerosis and inversely with IGFBP-3, a known in vitro PSA substrate. Androgen-stimulated LNCaP growth is inhibited by recombinant IGFBP-3 and by serine protease inhibitors which augment levels of secreted IGFBP-3.

Conclusion: The osteoblastic phenotype of metastatic prostate cancer correlates with intralesional activity of an IGFBP-3 protease, most likely PSA. We submit that drugs modulating the effects of IGFBP proteases represent a new approach to the treatment of refractory prostate cancer.

114 ORAL

The influence of previous hormone therapy on PSA response in prostate cancer patients (PTS) failing first-line androgen ablation

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Introduction: Liazal is a retinoic acid metabolism blocking agent (RAMBA) which promotes malignant cells to differentiate, by increasing endogenous RA in tumours. In a randomised phase III study the efficacy of Liazal 300 mg b.i.d. was compared with cyproterone acetate (CPA) 100 mg b.i.d. The influence of the type of previous androgen ablation on PSA response rate (PSA-RR) and time to PSA progression (TTP_{PSA}) was evaluated.

Results: Three hundred twenty-one pts were entered in the LIA-INT-5 trial. In total, 262 pts were evaluable for PSA response; 31 pts had a PSA response (at least 50% decrease from baseline), 25/127 pts on Liazal and 6/135 pts on CPA. No differences in the PSA parameters were observed between the pretreatment groups (Table). When correcting for each of the pretreatments Liazal proved to be consistently superior to CPA (all p = 0.04).

First-line therapy	Pts n	PSA-RR n	PSA-RR %	TTP_{PSA} (median – days)	
ORX	170	23	14%	117 d	(p = 0.7)
LHRH	92	8	9%	124 d	
PAB	190	19	10%	147 d	(p = 0.6)
MAB	72	12	17%	91 d	
FLU+	66	8	12%	120 d	(p = 0.8)
FLU–	196	23	12%	118 d	

Conclusion: Liazal is effective therapy in prostate cancer patients failing first-line hormone therapy. The observed PSA-RR was independent of previous first-line therapy. In particular, flutamide withdrawal did not account for the PSA responses.

115 ORAL

Immediate hormonotherapy with an LHRH analogue improves local control and survival in patients with locally advanced prostate cancer treated by radiotherapy. A randomized phase III clinical trial of the EORTC

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Aim of the Study: To increase the survival of patients suffering from locally advanced prostate cancers (T1–2, grade 3 N0-X, T3-4 N0-X, M0 according to the 1983 TNM clinical staging) by combining an external irradiation and an adjuvant hormonotherapy initiated at the very start of the treatment by improving the control of the disease in the pelvis and decreasing the occurrence of metastases outside the pelvis. Patients will be randomly allocated between the combined approach and radiotherapy alone, followed by the same hormonotherapy in case of further relapse whatever its site.

Treatment: In both arms, 50 Gy were delivered to the pelvis in 5 weeks, 5 days per week and 20 Gy in 2 weeks as a prostatic boost. The technique used for the whole treatment was a four field box technique. Hormonotherapy (arm 2) is given by a subcutaneous injection of an LHRH analogue (goserilin, 3.6 mg) every 4 weeks continued for a period of 3 years, the first injection starting on the first day of irradiation; besides, an anti-androgen was given orally (cyproterone acetate, 150 mg per day) starting once week before the onset of zoladex to inhibit the transient rise of testosterone, which might have deleterious effects.

Results: In the period 1987–1995, 415 patients under 81, were randomized. At the closure of the study 385 patients were evaluable for preliminary analysis: 190 (arm 1), 195 (arm 2). The median age was 71 years (range 51–80). Clinical, pathological biological characteristics of the patients were well balanced in the two cohorts. After a median follow-up of 42 months, 5-year local control and overall survival were significantly improved in the combined treatment arm ($p < 0.001$), which had not been shown so far.

Conclusion: These preliminary results suggest that adjuvant LHRH analogue (goserilin) started at the onset of external irradiation improves local control and survival.

116 ORAL

An EORTC phase III study comparing orchidectomy (Ctr) and orchidectomy plus mitomycin C (Exp: 15 mg/m^2 intravenously q6 wks until progression) with respect to quality of life in patients with poor prognosis M1 prostate cancer

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Purpose: To investigate the QL of M1 prostate cancer patients randomized to Exp as compared to Ctr.

Methods: A modified version of the EORTC QLQ-C30 was used to assess QL. The questionnaire included 2 of the QLQ-C30 functional scales (physical, role); 3 symptom scales (fatigue, pain and nausea/vomiting); the global health/QL scale and 5 single item scales (dyspnoea, insomnia, appetite loss, constipation and diarrhoea). Five additional questions assessing micturition were also included. The planned schedule of assessment was: at randomization, q6 weeks during the first nine months, every three months thereafter until progression of disease. A combination of descriptive graphical procedures and overall tests using summary measures were performed to describe the QL results.

Results: Between February 1990 and May 1995, 189 patients were randomized, 93 pts to Ctr and 96 to Exp. Overall survival was significantly shorter for patients on Exp. No significant difference was observed for progression-free survival. Compliance to QoL assessment was similar between the two treatment groups and ranged between 55–100% during the first year. A significant advantage for Ctr was observed in the Global health status/QL, fatigue, nausea/vomiting, dyspnoea and appetite loss scores.

Conclusion: The study indicated that mitomycin C in addition to orchidectomy is associated with a poorer QL and decreased survival.