880 POSTER

Prostate cancer cell proliferation is strongly reduced by combination treatment with the epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 ('iressa') and the anti -androgen bicalutamide ('casodex')

M. Bologna[1,2], A. Angelucci[2], C. Festuccia[2], G.L. Gravina[3], P. Muzi[2], C. Vicentini[3]. [1] *University of L'Aquila, Department of Basic and Applied Biology, L'Aquila, Italy;* [2] *University of L'Aquila, Department of Experimental Medicine, L'Aquila, Italy;* [3] *University of L'Aquila, Department of Surgery, L'Aquila, Italy*

Background: Polypeptide growth factors are modulators of prostate growth and function. EGF and TGF-α, ligands for the epidermal growth factor receptor (EGFR), are strong mitogens for prostate epithelial and stromal cells. Phosphorylation of EGFR is an important early event in signal transduction leading to tumor cell proliferation and invasion, and compounds blocking EGFR activation have been developed as anticancer agents. ZD1839 ('Iressa') is an orally active, selective EGFR-TKI (tyrosine kinase inhibitor) that blocks signal transduction pathways implicated in proliferation and survival of cancer cells. In this work, we assessed the effects of ZD1839, alone and in combination with the antiandrogen bicalutamide ('Casodex'), on proliferation of androgen-dependent prostate cancer cell lines.

Materials & Methods: We used three human cell lines: two androgen-receptor-positive and androgen-sensitive cell lines (ND1 and LNCaP) and one androgen-receptor-positive and androgen-insensitive cell line (ALVA-31).

Results: EGFR was expressed and phosphorylated in our cell system and ZD1839 was able to inhibit EGFR phosphorylation with IC50s ranging from 0.4 to 0.8 μM. In addition, ZD1839 inhibited cell proliferation with IC50s ranging from 0.37 to 0.9 μM in the same conditions. The IC50 was strongly decreased (about 10-fold) after treatment with low doses (< IC10) of antiandrogens such as bicalutamide; moreover, the IC50 for bicalutamide decreased about 5-fold after treatment with low doses (< IC10) of ZD1839. These superadditive effects may be associated with two major characteristics of prostate tumors. Firstly, EGFR can mediate an androgen-independent androgen receptor (AR) transactivation through its phosphorylation by several EGFR effectors. In fact, it has been shown that in androgen-depleted conditions the expression of PSA (which is modulated by AR) can be elevated and induced by EGFR ligands. Secondly, EGFR expression is increased after androgen ablation *in vivo*; *in vitro*, we have observed an increase of EGFR expression up to levels comparable to those of androgen independent cells in AR-transfected DU145 cell lines treated with antiandrogen.

Conclusions: These data represent a preliminary rationale for the possible clinical evaluation of ZD1839 in combination with bicalutamide in androgen-dependent tumors; the concurrent dual inhibition of AR and EGFR pathways might significantly slow down the onset of EGFR-driven androgen independence.

'Casodex' and 'Iressa' are trademarks of the AstraZeneca group of companies

881 POSTER

Efficacy and tolerability of radiotherapy as treatment for bicalutamide-induced breast pain and gynaecomastia in prostate cancer

H. Van Poppel[1], C. Tyrrell[2], P. Van Cangh[3], F. Keuppens[4], T. Morris[5], L. Garside[5]. [1] *UZ Gasthuisberg, Department of Urology, Leuven, Belgium;* [2] *Plymouth Oncology Centre, Plymouth, UK;* [3] *St Luc University Hospital (UCL), Brussels, Belgium;* [4] *Teaching Hospital of the Free University of Brussels (AZ-VUB), Brussels, Belgium;* [5] *AstraZeneca, Macclesfield, UK*

Background: Antiandrogen monotherapy is associated with gynaecomastia and breast pain due to an imbalance in the stimulatory effect of oestrogen and the inhibitory effects of androgens in the breast. The aim of this open-label, non-comparative, multicentre study was to assess the efficacy and tolerability of localised radiotherapy for the treatment of gynaecomastia and breast pain in men receiving 'Casodex' (bicalutamide) 150 mg monotherapy for management of their prostate cancer.

Methods: This study included patients with non-distant metastatic adenocarcinoma of the prostate (T1b-T4, NX, M0). All patients received bicalutamide 150 mg once daily and those who developed symptomatic gynaecomastia or breast pain were given radiotherapy soon after their symptoms started. Radiotherapy was administered as two fractions of electron-beam radiation given on consecutive days. Each fraction was 6 Gy (6-12 MeV, according to patient build), directed to irradiate a 5-cm diameter around each nipple and to treat from the skin surface down to the underlying muscle. At follow-up visits at 3 and 6 months, patients were questioned about gynaecomastia and breast pain.

Results: Fifty-one patients were included in the trial and received bicalutamide 150 mg. Of these, 72.5% of patients experienced gynaecomastia and 80.4% of patients experienced breast pain, both developing mostly within the first 6 months of bicalutamide 150 mg treatment. The majority of patients experienced mild gynaecomastia (64.7%) or breast pain (72.5%). Of those who received radiotherapy, 9 patients (33.3%) experienced an improvement or resolution of gynaecomastia and 15 patients (39.5%) had an improvement or resolution of breast pain. Radiotherapy-related adverse events were experienced by 43.9% of patients and all were short-lived (approximately 5 weeks' duration). Erythema was the most frequent adverse event, followed by skin irritation. The majority of the cases of erythema were mild, as were most cases of skin irritation; the remaining cases were moderate in severity.

Conclusions: For around one-third of patients, radiotherapy can reduce or ameliorate the intensity of 'Casodex' (bicalutamide)-induced symptomatic breast pain and gynaecomastia. Therapeutic radiotherapy using two fractions of 6 Gy electron-beam radiation to the male breast is well tolerated, with adverse events being generally mild and short-lived.

'Casodex' is a trademark of the AstraZeneca group of companies

882 POSTER

Is a short course of neoadjuvant/concurrent androgen deprivation beneficial for prostate cancer patients treated with a locally dose escalated radiation protocol?

A. Martinez[1], R. Galalae[2], C. Mitchell[1], N. Nuernberg[2], G. Gustafson[1], G. Edmundson[1], G. Kovacs[2]. [1] *William Beaumont Hospital, Radiation Therapy, Royal Oak, USA;* [2] *University Hospital Schleswig-Holstein, Campus Kiel, Radiation Therapy (Radiooncology) and Urology, Kiel, Germany*

Purpose/Objective: To address the survival influence of a short course of adjuvant/concurrent androgen deprivation therapy (ADT) in patients with localized prostate cancer treated to a very high local dose using high dose rate brachytherapy (HDR-BT).

Materials& Methods: The pooled data of two institutional prospective trials were analyzed including 579 patients treated since 1986 for clinically localized prostate cancer. The patients were treated with pelvic external beam radiotherapy and conformal interstitial HDR-BT boost. From those 378 patients were treated at William Beaumont Hospital, and 201 patients at Kiel University. In total 222 patients received androgen deprivation therapy for a period of ≤6 months. All patients with a follow-up ≥18 months (3 times greater than the exposure to ADT) were selected for this analysis leaving a total sample of 475 patients: ADT (n=151), no ADT (n=324). All patients had at least one of the following poor prognostic factors: Stage ≥T2b, Gleason score ≥7 and initial PSA of ≥10 ng/ml. The ASTRO definition for biochemical failure (BF) was used. Uni- and multivariate survival analyses were performed. A subgroup analysis stratified by ADT and poor risk factor was also calculated.

Results: The mean follow-up time for all patients was 5.1 years (range 1.5 14.5). The 5-year overall survival (OS) rate for all patients was 89%: 87% for ADT, and 90% for no ADT patients (p =0.437), The 5-year cause-specific survival (CSS) for all patients was 97%: 93% for ADT, and 98% for no ADT patients (p=0.015). The 5-year biochemical control (BC) for all patients was 79%: 80%for ADT, and 79% for no ADT patients (p=0.605). The detected negative survival impact of ADT was most prominent in the patient group (n=123) with all three poor prognostic factors: CSS 86% for ADT versus 96% for no ADT patients (p=0.009). Univariate analysis of BC revealed significant lower survival for high T-stage, high Gleason score, high initial PSA, and high # of poor prognostic factors. Multivariate analyses detected low age, high T-stage, and high Gleason score significant for biochemical failure. The addition of ADT was not significant either in univariate or in multivariate analyses.

Conclusion: The long-term outcome in terms of survival in patients with unfavorable prostate cancer following pelvic external beam radiotherapy and conformal interstitial HDR-BT boost is excellent. The addition of a short course of neoadjuvant/concurrent ADT to this treatment protocol delivering very high biological equivalent doses was not beneficial. In the opposite it resulted in lower CSS in very high-risk patients.