166

ENZYME INHIBITORS IN HORMONE DEPENDENT PROSTATE CANCER TREATMENT

A.A.Geldof, H.J. de Voogt and B.R.Rao
Dept.Endocrinol. Acad Ziekenh.V.U., P.O.Box 7057, 1007 MB Amsterdam, The Netherlands.

Presently, the traumatic castration procedure to achieve androgen withdrawal in the treatment of hormone dependent prostate cancer could be circumvented using a number of approaches. One of the options is to inhibit the enzymes involved in the synthesis of androgens. 4-MA (a 4-Methyl-4-Aza synthetic steroid) is known as a potent 5 alpha reductase inhibitor. In addition to Epostane (WIN 32,729) a known inhibitor of 3ß-hydroxysteroiddehydrogenase (3ß-HSD) activity, we discovered that 4-MA is also a potent 3ß-HSD inhibitor.
Both these compounds were tested for their effect on the growth rate of androgen dependent prostate cancer (R3327-H) in male Copenhagen rats. No significant tumor growth inhibitory effect was observed after the use of Epostane (within a six weeks period). 4-MA on the contrary significantly reduced the tumor growth rate. At the same time no change in serum testosterone levels in the 4-MA treated animals was noted.
It is concluded that the observed effect on tumor growth rate was determined solely by the 5-alpha reductase inhibitory activity. Administration of 5-alpha reductase inhibitor may be an effective endocrine treatment modality in the management of hormone dependent prostate cancer and it appears not to disturb other endocrine organ functions.
Acknowledgements: Mr.M.P.A.Meulenbroek and Mr.S.Bohlken for experimental assistence, The Netherlands Cancer Foundation, the Nijbakker Morra Stichting, the Maurits en Anna de Kock Stichting, the Stichting Bijstand Universitair Urologisch Onderzoek and the Academisch Ziekenhuis Vrije Universiteit for research support.

167

AROMATASE INHIBITION IN ADVANCED PROSTATIC CANCER

J.H.Davies, M.Dowsett, R.J.Shearer

We have previously shown the benefit of aminoglutethimide (Ag) and corticosteroids in advanced hormone insensitive prostate cancer. Hormone studies have shown that any suppression of adrenal androgens is produced by corticosteroids and that any additional benefit from Ag is not associated with further androgen depri vation. We have therefore sought another explanation for the action of Ag. Aromatase is inhibited by Ag and this could be its mode of ac tion. 4-hydroxyandrostenedione (4-OHA) is a more selective steroid aromatase inhibitor and we have evaluated it in 2 trials of patients with advanced prostate cancer. Subjective response was evaluated by the ECOG score, objective assessment was performed in trial 2 by transrectal ultrasound, bone scans, phosphatas es and PSA. 28 of 49 patients showed subjective response (56%)and 4 patients (8%) partial objective response. Side effects were few but 17 (34%) patients experienced a tumour flare after the first injection.
We discuss the mode of action of 4-OHA and the role of aromatase inhibition on prostatic disease both benign and malignant.
Institute of Cancer Research and Department of Urology, Royal Marsden Hospital, London, SW3 United Kingdom

168

Medroxyprogesterone acetate in advanced prostate cancer resistant to conventional therapy.

Robin Murray & Paula Pitt,
Cancer Institute, Melbourne Australia.

AIMS. To determine the efficacy of medroxyprogesterone acetate (MPA - "Farlutal" Farmitalia) in patients with advanced prostate cancer resistant to conventional therapy.

PATIENTS & METHODS. Seventy six men (medium age 69.5, range 49-82 years) with histologically proven progressive advanced carcinoma of the prostate, who had all had an orchidectomy and/or oestrogen therapy, were treated with 500mg. MPA/day. Assessment of response was according to NPCP criteria as modified by Citrin et al. Performance status was assessed according to ECOG criteria.

RESULTS.

	Remission	Stable Disease	Progression	Unassessable
No. patients	11	4	45	16
% response	14	5	59	21

If the unassessable patients are excluded the remission rate becomes 18.3% and the rate of stabilization 6.7%. Median duration of remission was 7.5 months (range 3-17.5). Median survival from commencement of treatment was 7.8 months for all patients, 9 months for remitters and 5.8 months for non-remitters (NS).

Performance Status on treatment	Improved	30%
	Unchanged	53%
	Deteriorated	12%
	Unknown	5%
Toxicity : (% of patients)	None	72
	"Flare"	18
	Vascular	5
	Gastric	6
	Diabetic	1

CONCLUSION.
MPA appears to offer useful benefit in up to 25% of patients with advanced prostatic cancer resistant to standard therapy, with remissions of between 3 & 18 months.

169

EFFECT OF TESTOSTERONE ON RAT SEMINAL VESICLE ALFA1RSV CELL PROLIFERATION,AND v-HaRAS AND v-KiRAS DERIVATIVES.

P.Correale,M.Marchese§,S.Pepe,B.Fiorentino,N.Normanno A.Contegiacomo,A.Budillon,P.Tagliaferri,A.R.Bianco,S. Metafora§.Cattedra di oncologia medica,Universita di Napoli §IIGB Napoli,Italy.

Understanding the possible relationship occurring between neoplastic trasformation and cell response to steroidal hormones can be of major interest. Human breast cancer MCF7 cells lose hormone sensitivity after trasfection with v-Ha ras oncogene (Kasid et al.Science 1986).We have identified an epithelial cell line derived from rat seminal vesicle, ALFA-1RSV,responsive to TST treatment.TST 0.1nM induces cell growth and increase H3-Thimidine uptake at 24h.Derivative clone ALFA-1KiKi trasformed with v-Kiras is responsive to TST treatment at 10nM concentration with a 100 fold reduced sensitivity to the hormon.However TST induces cell growth and increase H3 Thimidine uptake 6h after TST treatment.An evident increase in %S phase cells is observed with flow cytometric analysis 24/48h after TST treatment. TST effects on cell proliferation are completly neutralized on both lines ALFA-1RSV and ALFA-1KiKi by cyproterone, a receptorial antagonist of androgen.V-Haras transformed ALFA-1Ha cells are competely insesitive to TST growth stimulatory effect.Rat seminal vesicle cell sensitivity to androgen hormones is therefore affected by transformation with ras oncogene.

Supported by AIRC.