Pergamon

European Journal of Cancer Vol. 31A, No. 6, pp. 871–875, 1995

0959–8049/95 $9.50+0.00

0959-8049(95)00233-2

Papers

A Case for Synchronous Reduction of Testicular Androgen, Adrenal Androgen and Prolactin for the Treatment of Advanced Carcinoma of the Prostate

A. Rana, F.K. Habib, P. Halliday, M. Ross, R. Wild, R.A. Elton and G.D. Chisholm*

The present study was undertaken mainly to investigate whether prolactin manipulation combined with maximal androgen blockage improves the effectiveness of treatment in advanced prostatic cancer. The efficacy of oral hydrocortisone as an alternative to commercial anti-androgens in reducing the adrenal androgens, and of bromocriptine in reducing the prolactin level were also examined. A consecutive series of 30 patients with untreated and advanced prostatic cancer were entered into a three-arm prospective randomised trial. 10 patients received subcapsular orchiectomy alone (arm 1), another 10 had subcapsular orchiectomy plus flutamide (arm 2), and the remaining 10 had subcapsular orchiectomy plus oral hydrocortisone and bromocriptine (arm 3). Clinical and biochemical parameters, including trans-rectal ultrasound-determined prostatic volumes, hormonal profiles and radionuclide bone scan were evaluated at regular intervals. At 12 months, serum testosterone was reduced by more than 90% in all arms, however, maximum suppression of androstenedione, prolactin, and reduction of prostatic volumes were only observed in arm 3; this was reflected by the significant improvement in clinical response in arm 3 compared with other arms. This study suggests that a combined maximal suppression of androgens and prolactin offers a significant improvement in response over conventional treatments without prolactin suppression in the treatment of advanced prostatic cancer. Importantly, a better clinical outcome in arm 3 was still apparent at the end of 36 months.

Key words: androgen blockade, dopamine agonist, prostate cancer
Eur J Cancer, Vol. 31A, No. 6, pp. 871–875, 1995

INTRODUCTION

APPROXIMATELY 50% of men with prostatic cancer have metastatic disease at the time of presentation [1]. There is no firm consensus on whether any form of hormonal treatment improves the prognosis in this group of men.

Since Huggins and colleagues [2] demonstrated the beneficial response following orchiectomy or oestrogen treatment in 1941, the medical community has used various methods of hormonal manipulation in advanced carcinoma of the prostate (CaP). Recently, a theory of adrenal androgen hypersensitivity rather than androgen resistance has been advocated by Labrie and colleagues [3, 4] to explain the poor response or relapse after initial response following medical or surgical orchiectomy. They claimed a "dramatic response" following simultaneous reduction of testicular and adrenal androgens in men with advanced CaP. Since then, numerous large clinical trials have compared testicular androgen blockade with total androgen blockade but the results are mixed, even contradictory [5–8]. The cost of treatment has also become an important factor in the choice of treatment. If the outcome does not match the objectives, a costlier practice cannot always be justified and this has led to the search for alternatives. The use of oral glucocorticoids for suppression of adrenal androgens has received increasing interest in the treatment of advanced CaP [9–13]. It is not only cheaper

Correspondence to Dr F.K. Habib at the University Department of Surgery/Urology, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, U.K.
A. Rana, F.K. Habib, P. Halliday and M. Ross are at the University Department of Surgery/Urology; R. Wild is at the Department of Radiology; and R.A. Elton is at the Medical Statistics Unit, Western General Hospital, Edinburgh, U.K.
Received 19 Jan. 1995; accepted 10 Apr. 1995.

but some studies have also demonstrated better response when compared with commercial anti-androgens [12, 13].

Prostate cancer is the most hormone-sensitive cancer in man, thus the role of hormones other than testicular and adrenal androgens needs further exploration. Prolactin is another important hormone which has attracted clinical and research interest [14–17]. A rising serum prolactin level is a poor prognostic sign in patients with advanced CaP [18–20]. Thus, there is a body of evidence to support a contributory role for prolactin in the pathogenesis of prostatic cancer.

In an attempt to establish whether prolactin manipulation combined with maximal androgen blockade improves the effectiveness of the treatment of prostate cancer, a three-arm study was planned to compare bilateral orchiectomy alone in one arm, combined androgen blockage in the second, and orchiectomy plus hydrocortisone (HC) and bromocriptine (BC) in the third arm of patients with advanced CaP. The efficacy of oral HC as an alternative to other commercial anti-androgens in reducing the adrenal androgens, in combination with BC to reduce the circulating prolactin levels, was also examined in the present study.

PATIENTS AND METHODS

Patients

A consecutive series of 30 patients with untreated advanced CaP was entered into a prospective study between 1990 and 1991. Subcapsular orchiectomy was performed on all 30 men. 10 had no additional treatment (arm 1), 10 had combination treatment with flutamide (250 mg × tds) (arm 2) and the remaining 10 had combination treatment consisting of HC (30 mg/day) and BC (5 mg × tds) (arm 3). Patients were eligible for inclusion in the trial if they had untreated, histologically confirmed CaP and were either metastatic (M1) or locally advanced (T3/T4) with serum prostate specific antigen (PSA) greater than 40 ng/ml. Patients with an endocrine disorder, hypertension or on prolactin-stimulating drugs were excluded. Treatment was undertaken for a minimal period of 12 months. This study was approved by the Lothian Health Board Ethical committee.

Throughout the treatment, the clinical, haematological and biochemical parameters for each patient including serum PSA (Tandem-R), and urinary flow rates were evaluated every 3 weeks and then every 3 months. Bone scan, skeletal and chest X-rays were performed every 6 months or earlier, if indicated. Hormonal profiles and transrectal ultrasound (TRUS)-determined prostatic volumes were monitored up to the first 12 months of treatment. PSA measurement was continued up to 36 months.

Study design

Pretreatment evaluation was performed and informed consent was obtained. Patients were randomised by asking each individual to select a sealed envelope containing one of three treatments.

An increase in serum PSA of 4 ng/ml, local progression which required a transurethral resection (TUR) of primary tumour, metastatic progression requiring regular analgesics, radiotherapy or neurosurgical intervention, and cause-specific deaths were all considered objective progression. In addition, other established criteria of response (National Prostatic Cancer Project (NPCP)-criteria) were taken into consideration [21]. Prostatic volume was determined by TRUS using the prolate spheroid formula for up to 80 g glands and the spherical formula was used for larger glands [22]. A 50% or greater reduction in volume was mandatory for objective response. The need for transurethral resection of prostate (TURP) was based on bladder outflow symptoms as well as objective measurements such as urinary flow rate and ultrasound scan for residual volumes. The final decision for TURP as well as the operative procedure was performed by independent urologists not involved in this study. In the event of death, the certified cause of death was sought from the patient's own doctor.

Serum hormone measurements

All blood samples were taken at 14.00–16.00 hours, sera were separated and stored at −20°C prior to analysis for testosterone (T), androstenedione and prolactin (PRL) by radioimmunoassay. Samples from each patient were grouped and measured in one assay. Serum prolactin and testosterone were measured as detailed previously [23, 24]. Androstenedione was measured by radioimmunoassay employing an androstenedione RIA kit (Amersham, Bucks) with an interassay coefficient of variation (CV) of 9.6%.

Statistics

Paired Student's *t*-tests were used to analyse the significance of change in hormone concentrations and of prostatic volumes between pre- and post-treatment at 12 months. Changes in hormone levels and prostate volumes from pretreatment to 12 months were also compared between the different arms by two-sample *t*-tests. Furthermore, the two-tailed Fisher's exact test was used to compare the groups for response rate at 12 months.

RESULTS

Details of the hormonal profiles over the 12 month period for the three arms of treatment are shown in Figures 1–4. At 12 months, serum testosterone was reduced by more than 90% in all three arms (Figure 1). Adrenal androgen suppression with hydrocortisone was achieved with maximal reduction (84%) of androstanedione in arm 3 and this change was significantly greater than that in either arm 2 ($P = 0.048$) or in arm 1 ($P = 0.002$) (Figure 2). A maximal reduction (76%) in serum prolactin was also achieved in arm 3 which was significantly greater than those in arms 1 and 2 ($P = 0.002$ and $P < 0.001$, respectively) (Figure 3). Based on a PSA rise of >4 ng/ml, 2 patients in arm 1, one patient in arm 2 and 2 patients in arm 3

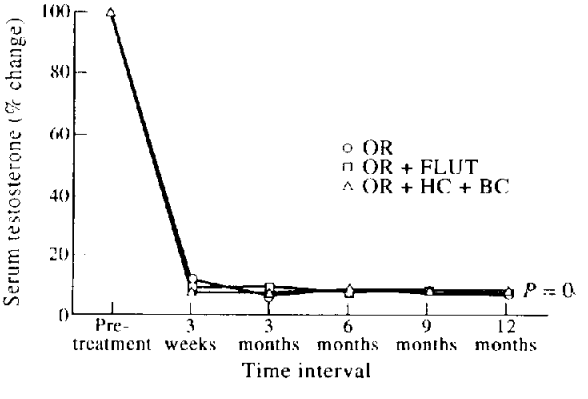

Figure 1. Change in mean serum testosterone at different time intervals following hormonal manipulations in advanced CaP. *P*-value refer to changes from pretreatment to 12 months in each group separately.

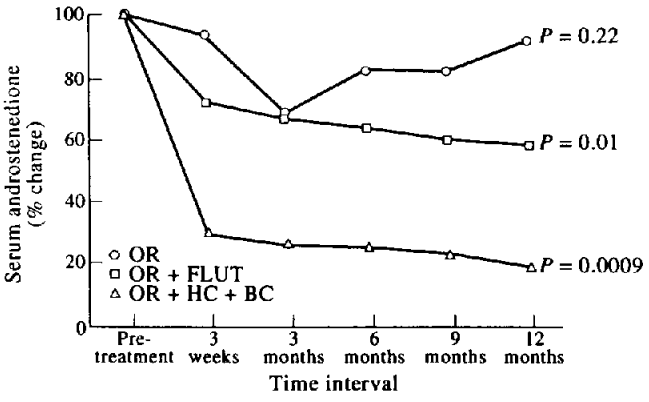

Figure 2. Change in mean serum androstenedione at different time intervals following hormonal manipulations in advanced CaP. *P*-values refer to changes from pretreatment to 12 months in each group separately.

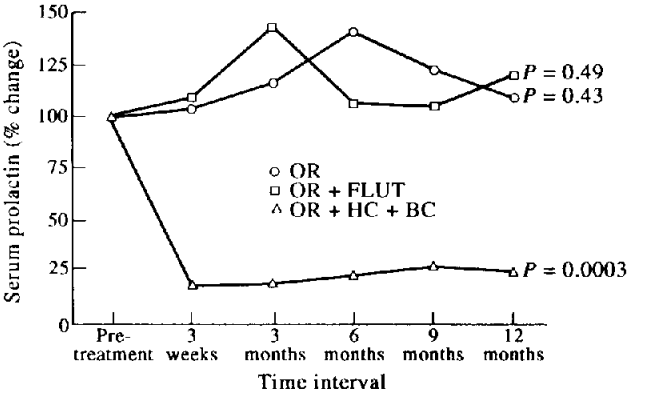

Figure 3. Change in mean serum prolactin at different time intervals following hormonal manipulations in advanced CaP. *P*-values refer to changes from pretreatment to 12 months in each group separately.

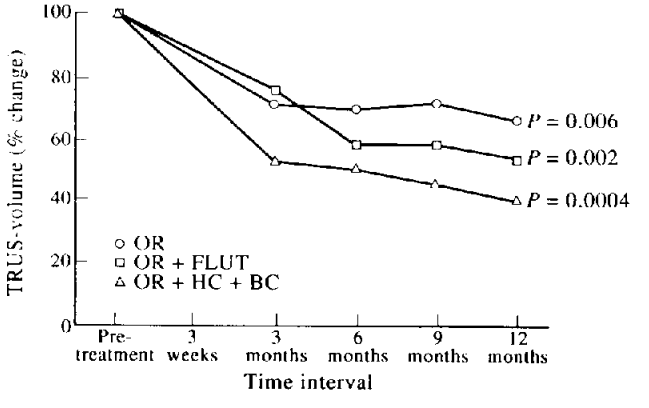

Figure 4. Change in mean prostatic volumes at different time intervals following hormonal manipulations in advanced CaP. *P*-values refer to changes from pretreatment to 12 months in each group separately.

showed evidence of disease progression during the first year of treatment. At the end of 3 years this had increased to 6 patients in arm 1, and 4 patients in both arms 2 and 3.

In addition to the changes in hormone concentrations with treatment, we also noted a reduction in primary prostatic volume following endocrine therapy and this was maximal in arm 3 (mean ± S.E. = 61 ± 3.1%) when compared with either arms 1 (35 ± 13.4%) or 2 (48 ± 6.4%) (Figure 4); however, there was no statistical difference between any of the groups.

A summary of the objective and clinical responses at 12 months for each of the patients entered in the study is outlined in Table 1. The partial or complete response rate was comparable in arm 1 (3/10) and 2 (1/10; $P = 0.29$) but this was significantly

Table 1. Summary of clinical response within 12 months of hormonal manipulation in patients randomised into each of three treatment arms

Arm 1 (orchiectomy)		
Patient	1	Required radiotherapy, neurosurgery and eventually died of prostate cancer at 9 months (approx)
	2	Partial response
	3	Partial response
	4	Died of prostate cancer at 9 months
	5	Partial response
	6	On regular analgesics for bone pain
	7	Abnormal PSA
	8	On regular analgesics plus abnormal PSA
	9	On regular analgesics plus outflow symptoms plus required TURP
	10	Abnormal PSA plus outflow symptoms plus required TURP
Arm 2 (orchiectomy plus flutamide)		
Patient	1	On regular analgesics plus abnormal PSA
	2	On regular analgesics
	3	Outflow symptoms and poor flow rate
	4	Outflow symptoms plus required TURP
	5	On regular analgesics plus hot spots on bone scan
	6	Abnormal PSA
	7	Partial response
	8	Outflow symptoms plus required TURP plus worse performance status
	9	On regular analgesics plus required TURP and eventually died of prostate cancer at 6 months (approx)
	10	Outflow symptoms plus required TURP
Arm 3 (orchiectomy plus HC plus BC)		
Patient	1	Abnormal PSA*
	2	Partial response
	3	Partial response, non-cancer death
	4	Partial response
	5	Partial response
	6	Partial response
	7	Partial response
	8	Complete response (widespread bone metastases normalised within 12 months)
	9	Partial response
	10	Abnormal PSA†

HC, hydrocortisone; BC, bromocriptine; *BC was reduced to half dose for possible link with hallucination in this 85-year-old man. It was later found out that he had similar problems prior to hormonal treatment; †This man has a grossly deteriorated renal function before treatment which improved significantly with treatment and remains symptom-free.

better in arm 3 (8/10 as compared with 4/20 in the other two groups combined; $P = 0.003$). Even if the conservative assumption was made that the partial responder in arm 3 who died from a non-cancer cause might have progressed within a year of treatment, the outcome in arm 3 at 12 months was still better ($P = 0.012$) than in arms 1 and 2. It is of note that one patient in arm 3 with "widespread bone metastases" had "normalisation" within 12 months of treatment. After 36 months, there have been 4 prostate cancer deaths in arm 1 and 2 in arms 2 and 3. A better clinical outcome in arm 3 is still apparent (Table 2).

Table 2. Summary of clinical response within 36 months of hormonal manipulation in patients randomised into each of three treatment arms

Arm 1 (orchiectomy)		
Patient	1	Required radiotherapy, neurosurgery and eventually died of prostate cancer at 9 months
	2	Partial response
	3	Partial response
	4	Died of prostate cancer at 9 months
	5	Outflow symptoms plus required TURP
	6	Required radiotherapy and died of prostate cancer at 35 months
	7	Abnormal PSA, required radiotherapy plus TURP
	8	On regular analgesics, developed lung metastases and died of prostate cancer at 25 months
	9	On regular analgesics plus outflow symptoms plus required TURP
	10	Abnormal PSA plus required TURP, non-cancer death
Arm 2 (orchiectomy plus flutamide)		
Patient	1	Required analgesics plus radiotherapy, non-cancer death
	2	On regular analgesics
	3	Outflow symptoms, abnormal PSA and in long-term nursing care
	4	Outflow symptoms plus required TURP
	5	Required radiotherapy, died of prostate cancer at 30 months
	6	Abnormal PSA, required analgesics plus radiotherapy
	7	Partial response
	8	Outflow symptoms plus required TURP plus worse performance status
	9	On regular analgesics plus required TURP, died of prostate cancer at 6 months
	10	Outflow symptoms plus required TURP
Arm 3 (orchiectomy plus HC plus BC)		
Patient	1	Abnormal PSA, required radiotherapy and died of prostate cancer at 16 months
	2	Partial response
	3	Partial response, non-cancer death
	4	Complete response (PSA and bone scan normal)
	5	Partial response
	6	Abnormal PSA
	7	On regular analgesics plus required radiotherapy
	8	Complete response (widespread bone metastases normalised within 12 months)
	9	Partial response, non-cancer death
	10	Abnormal PSA, died of prostate cancer at 33 months

HC, hydrocortisone; BC, bromocriptine

DISCUSSION

The present study has compared three different approaches for hormonal manipulation in advanced CaP. Whilst some of our results confirmed the findings of earlier investigations [4, 13, 18, 19], we have also pinpointed the limitations of some of these therapies and highlighted the possible benefits of prolactin suppressing agents as adjuncts in the treatment of advanced CaP. We have shown that both testicular as well as combined androgen blockade treatments failed to produce a complete androgen-free milieu, leaving sufficient androgens to allow the prostate cancer cells to continue proliferating. However, it is not clear whether these residual androgens are solely responsible for the flare-up of the disease or whether this effect is potentiated by other factors. Earlier studies have shown that prolactin may be involved in prostate growth [14, 26–28] and later investigations have established the presence of prolactin receptors along the prostate cell membrane [29]. It is conceivable that these receptors might facilitate the entry of androgen into the prostate gland by inducing lipolysis of membrane phosphatides [30].

Because of this association between prolactin and the prostate, antiprolactin agents have been administered to patients with CaP [18–20]. Earlier trials demonstrated significant clinical benefits in androgen-escaped patients [31–34]. Based on these earlier reports, we introduced bromocriptine in the present series at a divided dose of 15 mg per day to produce a maximum prolactin suppression at the start of treatment.

Whilst there is a case for change from a limited androgen blockade with orchiectomy to the combined testicular and adrenal androgen blockade, the clinical benefits of androgen receptor-blockers such as flutamide or cyproterone acetate may not be as significant as originally envisaged in the treatment of advanced prostate cancer. Hence the cost of such treatment remains to be justified in a clinical context. Maximal androgen suppression has been possible by combining orchiectomy with a simple replacement dose of oral glucocorticoids as has been demonstrated in the present study which also reaffirms the previous reports [12, 13, 20]. When androgen concentrations are maintained at minimal level as with arm 3 of this study, then the androgen receptors remain inactive. This results in significant clinical benefits and offers the added advantage of being cost-effective.

Serial measurements of PSA and TRUS-determined prostatic volumes have minimised the subjective variations in the assessment of response to treatment [35, 36]. In the present study, we have relied on these parameters for response. Following use of prolactin suppressant as an adjunct to maximal androgen suppression, only 20% of patients in treatment arm 3 had disease progression at 12 months and this was solely on the grounds of elevated serum PSA (an increase of more than 4 ng/ml) despite the fact that they remained symptom-free (Table 1). At 36 months, again based on elevated PSA, only 40% of the patients in arm 3 had disease progression compared to 60% in arm 1. A median reduction of 47% in prostatic volume reported by Pinault and colleagues' series [36] corresponds to a mean reduction of 48% in our series with combined androgen blockade; however, a synchronous prolactin manipulation has had even more pronounced reduction (61%) of primary tumour volume, although the difference was not statistically significant.

In conclusion, the present study has enhanced our understanding of the hormonal control of prostatic cancer and reinforced the rationale for deliberate suppression of prolactin in conjunction with maximal androgen blockade in the treatment of

advanced CaP. A combined maximal suppression of androgens and prolactin has been tested and early results from this study have demonstrated significant improvement of clinical response over conventional treatments without prolactin suppression. This study provides evidence in support of the synchronous reduction of testicular androgen, adrenal androgen and prolactin from the start of treatment for advanced carcinoma of the prostate.

1. Sogani P, Fair W. Treatment of advanced prostatic cancer. *Urol Clin N Am* 1987, **14**, 353–371.
2. Huggins C, Stevens RE, Hodges CV. Studies on prostate cancer. II. The effect of castration on clinical patients with carcinoma of the prostate. *Arch Surg* 1941, **43**, 209–223.
3. Labrie F, Dupont A, Belanger A, *et al.* New approach in the treatment of prostate cancer: Complete instead of partial withdrawal of androgens. *The Prostate* 1983, **4**, 579–594.
4. Labrie F, Dupont A, Belanger A. Complete androgen blockade for the treatment of prostate cancer. In De Vita VT, Hellmann S, Rosenberg S, eds. *Important Advances in Oncology*. New York. J.B. Lippincott, 1985, 193–217.
5. Crawford ED, Eisenberger MA, McLeod DG, *et al.* A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 1989, **321**, 419–424.
6. Iversen P. DAPROCA.: Zoladex plus flutamide vs orchiectomy for advanced prostatic cancer. *Eur Urol* 1990, **18**, 41–44.
7. Tyrrell CJ, Altwein JE, Klippel F, *et al.* A multicenter randomised trial comparing the luteinising hormone-releasing hormone analogue Goserelin acetate alone and with flutamide in the treatment of advanced prostate cancer. *J Urol* 1991, **146**, 1321–1326.
8. Janknegt RA, Abbou CC, Bartoletti R, *et al.* Orchiectomy and nilutamide of placebo as treatment of metastatic prostatic cancer in a multinational double-blind randomised trial. *J Urol* 1993, **149**, 77–83.
9. Plowman P, Perry L, Chard T. Androgen suppression by hydrocortisone without aminoglutethimide in orchiectomised men with prostatic cancer. *Br J Urol* 1987, **59**, 255–257.
10. Dowsett M, Shearer RJ, Ponder B, Malone P, Jeffcoate SL. The effects of aminoglutethimide and hydrocortisone, alone and combined, on androgen levels in post orchiectomy prostatic cancer patients. *Br J Cancer* 1988, **57**, 190–192.
11. Tannock I, Gospodarawicz M, Meakin W, Panzarella T, Stewart L, Rider W. Treatment of metastatic prostate cancer with low dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol* 1989, **7**, 590–597.
12. Becker H, Klosterhalfen H. Clinical experience with androcur in the treatment of prostatic cancer. In Klosterhalfen H, ed. *Endocrine Management of Prostatic Cancer, New Developments in Biosciences*. New York, Watter de Gruyter, 1988, **4**, 121–126.
13. Williams G, Asopa R, Abel PD, Smith C. Pituitary adrenal and gonadal endocrine suppression for the primary treatment of prostate cancer. *Br J Urol* 1990, **65**, 504–508.
14. Huggins C, Russell PS. Quantitative effects of hypophysectomy on testis and prostate of dogs. *Endocrinology* 1946, **39**, 1–7.
15. Grayhack JT, Bunce PL, Kearns JW, Scott WW. Influence of the pituitary on prostatic response to androgen in rat. *Bull John Hopkins Hospital* 1955, **96**, 154–163.
16. Farnsworth WE. In Boyns AR, Griffiths K, eds. *Prolactin and Carcinogenesis*. Cardiff, Alpha Omega Alpha, 1972, 217–218.
17. Weber MM, Perez-Ripoll EA. Prolactin in the aetiology and progression of human prostate carcinoma. *J Urol* 1986, **135**, 348A Abstr 978.
18. Mee AD, Khan O, Mashiter K. High serum prolactin associated with poor prognosis in carcinoma of the prostate. *Br J Urol* 1984, **56**, 698–701.
19. Morales A, Curtis-Nickel J. Clinical relevance of plasma testosterone and prolactin changes in advanced cancer of prostate treated with diethyl stilboestrol or estramustine phosphate. *Urology* 1985, **26**, 477–481.
20. Matzkin H, Kaver I, Lewyshon O, Ayalon D, Braf Z. The role of prolactin levels under GnRH analogue treatment in advanced prostatic carcinoma. *Cancer* 1988, **61**, 2187–2191.
21. Murphy GP, Slack NH. Response criteria for the prostate of the USA. National Prostatic Cancer Project. *Prostate* 1980, **1**, 375–382.
22. Terris MK, Stamey TA. Determination of prostate volume by transrectal ultrasound. *J Urol* 1991, **145**, 984–987.
23. Odoma S, Chisholm GD, Nicol K, Habib FK. Evidence for the association between blood prolactin and androgen receptors in BPH. *J Urol* 1985, **133**, 717–720.
24. Habib FK, Lee IR, Stitch SR, Smith PH. Androgen levels in the plasma and prostatic tissues of patients with benign hypertrophy and carcinoma of the prostate. *J Endocrinol* 1976, **71**, 99–107.
25. Grayhack JT, Bunce PL, Kearns JW, Scott WW. Influence of the pituitary on prostatic response to androgen in rat. *Bull John Hopkins Hospital* 1955, **96**, 154–163.
26. Yamanaka H, Kirdani RY, Saroff J. Effects of testosterone and prolactin on rat prostatic weight, 5 alpha-reductase, and arginase. *Am J Physiol* 1975, **229**, 1102–1109.
27. Boyns AR, Cole EN, Golder MP. In Boyns AR, Griffiths K, eds. *Prolactin and Carcinogenesis*. Cardiff, Alpha Omega Alpha, 1972, 207.
28. Jacobi GH, Altwein JE, Hohenfellner R. Adjunct bromocriptine treatment as palliation for prostate: experimental and clinical evaluation. *Scand J Urol Nephrol* 1980, Suppl **55**, 107–112.
29. Leake A, Chisholm GD, Habib FK. Characterisation of the prolactin receptors in human prostate. *J Endocrin* 1983, **99**, 321–328.
30. Dave JR, Witorsch RJ. Prolactin increases lipid fluidity and prolactin binding of rat prostatic membranes. *Am J Physiol* 1985, **248**, E687.
31. Sadoughi N, Razvi M, Bush I, Ablin R, Guinan P. Cancer of prostate. Relief of bone pain with levodopa. *Urology* 1974, **4**, 107–108.
32. Farnsworth WE, Gonder MJ. Prolactin and prostate cancer. *Urology* 1977, **10**, 33–34.
33. Jacobi GH, Sinterhauf K, Hurth KH, Altwein JE. Testosterone metabolism in patients with advanced carcinoma of the prostate: a comparative *in vivo* study of the effect of oestrogen and antiprolactin. *Urol Res* 1978, **6**, 159–165.
34. Farnsworth WE. *Prolactin*. In Farnsworth WE, Ablin RJ, eds. The prostate as an endocrine gland. Florida, CRC Press, 1990, 177–185.
35. Janknegt RA. Estramustine phosphate and other cytotoxic drugs in the treatment of poor prognostic advanced prostate cancer. *The Prostate* 1992, (Suppl) **4**, 105–110.
36. Pinault S, Tetu B, Gagnon J, Monfette G, Dupont A, Labrie F. Transrectal ultrasound evaluation of local prostate cancer in patients with LHRH agonist in combination with flutamide. *Urology* 1992, **39**, 254–261.