COMPLETE ANDROGEN BLOCKADE IN ADVANCED PROSTATE CANCER: A CLINICAL EXPERIENCE

Aminul Haq, Azra A. Ghani, Taskeen Ahmad Khan, Isa Khan

Department of Urology,
Postgraduate Medical Institute,
Lady Reading Hospital,
Peshawar.

ABSTRACT

Objective: To evaluate the clinical and biochemical outcome of patients with advanced prostate cancer treated by complete androgen blockage (CAB).

Material and Methods: A total number of thirty patients with histologically confirmed advance prostate cancer and serum PSA level of more than 30ng/ml were subjected to bilateral subcapsular orchidectomy, supplemented with oral antiandrogens. These patients were followed for a period of two years by recording their symptoms and serum PSA level at twelve weeks intervals.

Results: Only 16(53.33%) patients complied with the protocol of the study and observed two years followup. 12(75%) patients showed complete response to CAB while 4(25%) patients showed rising PSA levels and became symptomatic after one year of treatment.

Conclusion: CAB is still the treatment of choice for patients with advanced prostate cancer.

Key words: Advanced prostate cancer, Complete androgen blockade.

INTRODUCTION

Prostate cancer is androgen dependant and the established treatment for advanced disease involves hormonal manipulation to deprive the cancer of androgen stimulation. The most commonly used treatments are bilateral orchidectomy or medical castration using a leutinizing hormone-releasing hormone (LH–RH) analogue, both of which eliminate the androgen of gonadal origin. These treatments modalities can be used either alone or in combination with an anti-androgen, which inhibits the effect of androgens by blocking the androgen

receptors (combined androgen blockade, CAB)[1].

In many studies improvement in response to treatment and survival is reported in patients with advanced prostate cancer who receive CAB compared with castration alone[2,3,4,5]. However, other trials report no difference between CAB and castration alone[6,7].

Although many recent studies report no statistically significant difference in terms of subjective and objective response to CAB than castration alone[1,8,9], this treatment is still considered as the gold standard for advanced prostate cancer.

MATERIAL AND METHODS

Between January 1999 to December 2002 a total number of 30 patients with advanced prostate cancer having a mean age of 79.26 years were recruited for this study.

Patients with histologically confirmed stage-III locally advanced (PSA > 30 ng/ml) or metastatic disease who had given their informed consent were included in this study. Patients who were having low stage / grade of prostate cancer and having a PSA level of less than 30ng/ml and those having any history of hormonal ablation therapy were excluded from the study.

Digital rectal examination (DRE) was performed in all these cases, while histological evidence of malignancy was obtained by sextant biopsies of the prostate. Skeletal scientigraphy was also performed.

Bilateral sub-capsular orchidectomy was done in all patients under spinal anaesthesia and Flutamide tablets 250mg BD were supplemented orally as an anti-androgen. Follow-up of these patients were done by recording their symptoms and serum PSA levels at 12 weeks intervals.

RESULTS

Out of 30 patients only 16(53.33%) observed with the protocol of the study and complied the two years follow-up. The initial skeletal scientigraphy was positive in 27 (90%) cases. The baseline mean PSA level was 139.96 ng/ml while the Gleason grade as shown on histological examination was Gleason grade- III (Gleason sum 8-10) in 23(76.66%) cases and Gleason Grade – II (Gleason sum 5-7) in the remaining 7(23.34%) cases.

The mean volume of the prostate as assessed by trans-abdominal ultrasonography was 61.63cm$^{(3)}$. Cardiovascular problems caused death of 02(8.66%) patients after four months. Another 6(20%) were lost to follow-up. Of the remaining 22(73.33%) patients 6(20%) abondand oral anti-androgens due to its cost. These patients were followed for a period of two years by assessing their symptoms and estimation of serum PSA levels at 03 months intervals. Among these 16 patients, 4 showed a rise of PSA after one year and symptoms of bone pains as well, while in the remaining 12 patients the serum PSA level remained below 10ng/ml, up to their last follow-up. No symptoms of metastasis were recorded.

To test the significance of the difference between base line mean PSA level and the PSA level of the remaining patients who completed two years followup; student T-test was applied. The level of significance chosen as .001. A highly significant difference ($P<.01$) was observed in the PSA level of base line and the last PSA level of the reaming patients after drop out due to various causes.

Four patients who showed a rising PSA level after one year with CAB were offered intermittent androgen deprivation by initially withdrawing their oral anti-androgens and then restarting it after the PSA level was >

20ng/ml. They showed both subjective and biochemical response in terms of lower PSA trends but this response was observed for a period of only one year and then these patients became hormone refractory.

DISCUSSION

Since death due to carcinoma prostate is almost invariably a result of failure to control metastatic disease, a great deal of research has concentrated on the efforts to control distant disease. It is well known that most prostatic carcinomas are hormone dependant and that approximately 70 – 80% of men with metastatic carcinoma prostate respond to various forms of androgen deprivation[10].

Patients with advanced prostate cancer who receive combined androgen blockade (CAB) show better response to treatment, and survival[1]. Many recent studies are favouring mono-therapy with anti-androgens alone but show a definite significance in favour of CAB[11,12,13]. The data from the analysis by F. Boccardo et al; showed the hazard of progression of patients initially assigned to bicalutamide mono-therapy was 20% higher than those initially treated with castration, although the hazard of mortality remained the same for both groups.[11] Several studies have demonstrated that the early initiation of anti-androgens either alone or as a adjuvant therapy is associated with prolong survival in men with advanced prostate cancer[16,17].

In all the studies conducted so for on advanced prostate cancer, serum PSA has been used as a surrogate marker both to evaluate the progression of disease and the response to treatment[1,11,12,13]. Crook et al[14]; and Bruchovasky et al[15]; demonstrated the value of serum PSA levels in their series to monitor the response of androgen deprivation therapy.

Patients who receive CAB may show a rise of PSA level after some time when these patients enter into the hormone refractory prostate cancer. This is the group of patients who then respond to intermittent androgen deprivation[14].

In our study only 16 patients were followed for a period of two years. Out of these 16 patients 4(25%) showed a rising PSA level after a period of one year and this group then received intermittent androgen deprivation on the basis of PSA levels, as reported in some recent studies[14]. The responses in these patients were short lived and after one year the PSA levels were not influenced by androgen deprivation. These patients were then treated as hormone refractory cases. The remaining 12(75%) patients showed complete response to CAB and apart from the subjective improvement, the PSA levels also remained below 10ng/ml upto their last follow-up. We also initiated androgen deprivation therapy in our patients regardless of the symptoms of the patients as reported in literature[16,17].

No complications were recorded in our cases either from surgical procedures or use of anti-androgens except painful gynaecomastia in a few patients. Although there are reports of hepatotoxicity due to long term use of antiandrogens[11,12].

Our finding are consistent with those reported in the literature[3,5,9,12,13]. It is thus concluded from this study that CAB is still the treatment of choice for patients with advanced prostate cancer, but further studies are needed to evaluate the effects of mono-therapy with either Flutamide or castration alone and also the effects of intermittent androgen ablation in these patients. We also recommend early initiation of androgen deprivation therapy.

REFERENCES

1. Tyrrell CJ, Altwein JE, Jordman TP, et al. Comparison of an LH-RH Analogue (Zoladex) with combined Androgen Blockade in Advanced prostate cancer: Final survival results of an international multicentre randomized trial. Eur Urol 2000; 37: 205-11.
2. Denis LJWhelan P, Carneiro de Moura JL, et al. Goserelin acetate and flutamide versus bilateral orchidectomy: A phase III EORTC trial (30853). Urology 1993; 42: 119 -30.
3. Dennis LJ, Keuppens F, Smith PH, et al. Maximal androgen blockade: final analysis of EORTC phase III trial 30853. Eur Urol 1998; 33: 144-51.
4. Janknegt RA, Abbou CC, Bartotetti R, et al. Orchidectomy and nilutamide or placebo as treatment of metastatic prostatic cancer in multinational double blind randomized trial. J Urol 1993; 149: 77-83.
5. Dijkman GA, Janknegt RA, de Reigke TM, et al. Long term efficacy and safety of nilutamide plus castration in advanced prostate cancer, and the significance of early prostate specific antigen normalization. J Urol 1997; 158: 160-3 .
6. Ferrari P, Castagnetti G, Ferrari G, et al. Combination treatment in M1 prostate cancer. Cancer 1993; 7 (suppl 12): 3880-5.
7. Iversen P, Ransmussen F, Klarskov P, et al. Long terms results of Danish prostatic cancer group trail 86. Goserelin acetate plus flutamide versus orchidectomy in advanced prostatic cancer. Cancer 1993; 82 (suppl 12): 3851-4.
8. Tyrell CJ, Altwein JE, Klippel F, et al. A multicenter randomized trail comparing the lutenizing hormone releasing hormone nalague goserelin acetate alone and with flutamide in the treatment of advanced prostate cancer. J Urol 1991; 146: 1321-6.
9. Tyrell CJ, Altwein JE, Klippel F, et al. A multicentre randomized trial comparing goserelin acetate with goserelin acetate + flutamide in the treatment of advanced prostate cancer (survival update); in Murphy G, Khoury S, Chatelain C, Denis L editors. Proceedings of the 3rd International Symposium on Recent Advances in Clinical Cancer Diagnosis and Treatment, 1993, 98.
10. Presti JC Jr. Neoplasms of prostate gland. Smith General Urology 2000; 399.
11. Boecardo F. Bicalutamide monotherapy versus flutamide plus Goserlin in Prostate cancer: Updated results of a multicentric trial. Eur Urology 2002; 42: 481-90.
12. Tyrrell CJ, Kaisary AV, Iversen P, et al. A randomized comparison of 'Casodex™ (Bicalutamide) 150mg monotherpay versus castration in the treatment of metastatic and locally advanced prostate cancer. Eur Urol 1998; 33; 447 – 56.
13. Ivarson P, Typerell CJ, Kaisary AV, et al. Bicalutamide monotherapy with castration in patients with non metastatic locally advanced prostate cancer, 6.3 years of follow-up. J Urol 2000; 164; 1579 - 82.
14. Crook JM, Szumacher EF, Esche BE, et al. Intermittent androgen suppression in the management of prostate cancer. Urology 1999; 53; 530-4.
15. Bruchovsky N, Klotz LH, Crook JM, et al. A phase-II study of intermittent androgen suppression in men with a rising PSA after radiation for localized prostate cancer. J Urol 1998; 159; A 1287.
16. Granfors T, Modig H, Damber JE, et al. Combined orchiecdectomy and external radiotherapy versus radiotherapy alone for nonmetastatic prostate cancer with or without pelvic lymph node involvement: a prospective randomized study. J Urol 1998; 159: 2030-4.
17. The Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer; initial results of the Medical Research council Trial. Br J Urol 1997; 79: 235-46.

Address for Correspondence:
Dr. Aminul Haq,
Department of Urology,
Postgraduate Medical Institute,
Lady Reading Hospital, Peshawar.