

Research Article

Bilateral orchiectomy versus total androgen blockade in the management of metastatic cancer prostate

Rajesh*, D. K. Nigam

Department of Surgery, MRA Medical College Ambedkarnagar, UP, India

Received: 20 February 2016

Accepted: 25 February 2016

***Correspondence:**

Dr. Rajesh,

E-mail: drkumar64@gmail.com

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ABSTRACT

Background: Advanced prostatic cancer in India is mainly managed by bilateral scrotal orchiectomy. Though combined androgen blockade is advocated, its doubtful efficacy and high cost promoted us to undertake this study in Indian patients comparing bilateral orchiectomy plus placebo versus bilateral orchiectomy plus flutamide in improving overall survival in metastatic prostate cancer.

Methods: This 18 months observational study was conducted in the patients coming to the urology unit of department of Surgery, SN Medical College & Hospital Agra, with the symptoms of prostate cancer after taking permission from the Institutional Ethical committee. Methods of Palliation used were bilateral orchiectomy and Anti-androgen flutamide. Statistical analysis was done using SPSS and a p value of <0.05 was considered as statistically significant.

Results: A total of 12 previously untreated patients with osseous metastases confirmed by bone scan or skeletal survey, were entered into a double blind randomization placebo controlled trial of bilateral orchiectomy with or without total androgen blockade. The patients were followed up for eighteen months. One patient out of twelve in placebo group died due to early progressive disease. The mean percentage changes in placebo group was 68% and flutamide group was 73%, Showing no statistical difference in both groups (p-value>0.05). Over all response rate was 83.3% in both the groups. The adverse effect like hot flushes and diarrhoea was observed 33.3% in total androgen blockade in comparison to placebo controlled group having 16.6% only. Colonic origin of sepsis was associated with worse outcome probably due to presence of feculent exudates which was more commonly associated with colonic origin of sepsis. Female sex was associated with better outcome as compared to male sex. Our study differs from MPI in these 2 variables of adverse outcome.

Conclusions: It is evident that the addition of antiandrogen like flutamide to orchiectomy did not show any significant beneficial effect. The routine use of flutamide is not advisable due to its cost effectiveness.

Keywords: Bilateral orchiectomy, Total androgen blockade, Metastatic cancer prostate

INTRODUCTION

Among all cancers that arise in the prostate the most common is adenocarcinoma accounting for more than 95%. The etiology of prostate cancer remains unknown and no definite carcinogen is known to be responsible; a viral etiology has been suggested but not verified. It is possible that alternation in estrogen & androgen balance and metabolic alteration in prostate may play a role but

exact clinical significance in these changes remains to be established. A probable role for genetic factor in cancer prostate has also been uncovered previously in familial aggregations.¹ The management of carcinoma prostate is based on clinical examination, laboratory investigations such as serum PSA and histopathology and bone scan with treatment and close follow up of the patients.

The treatment of prostate cancer at present is selected on the basis of accurate anatomic definition of the stage of the disease. Early localized tumour which has not metastasized is treated by radical prostatectomy and radiation to eradicate the tumour. The metastatic lesion of prostate is generally managed by palliation. Because most of the tumours are hormones sensitive in nature, the modes of palliations are androgen withdrawal by medical or surgical castration, androgen blockade by anti-androgens like cyproterone acetate (CP), flutamide or bicalutamide, and combination treatment by maximum/total androgen blockade by medical/surgical castration plus antiandrogen.

The anti-androgen flutamide, a non-steroidal agent which competes with both testosterone and dihydrotestosterone for androgen receptors, is used commonly in maximum or total androgen blockade (TAB).

For metastatic prostate cancer bilateral orchiectomy has remained the "gold standard" of therapy since its introduction by Huggins et al in 1941.² But the median survival of the patient with metastatic disease is approximately two years and eighty percent of the patients die within five years despite therapy.

Testes are responsible for production of 95% of circulating androgens in the form of testosterone. Remaining 5% of circulating androgens are produced by the adrenals through production of dihydroepiandrosterone and androstendione. The androgens are secreted by the Leydig cells of the testes upon stimulation by luteinizing hormone (LH) secreted by the pituitary, in turn responding to the LH-RH released by the hypothalamus. Within prostatic cells, testosterone is converted to DHT by the action of 5 α -reductase. DHT is the active molecule, which binds to the androgen receptors in the prostatic cells and exerts its various actions. Each of these steps has been targeted for therapeutic strategies in management of prostatic cancer stage D2.

Albeit castration by orchiectomy or LH-RH analogues causes a 90-95% reduction in serum testosterone concentration, the active metabolite of testosterone. After castration, intraprostatic DHT concentration remains at approximately 40% of that measured in intact men. Therefore it appears logical to treat patients of prostate cancer by combined / Total androgen blockade- both testicular & adrenal androgen – a theory first propounded by Labrie et al in 1983.³

Contrary to this report, studies by Schroder and Iverson have showed no significant difference between the two arms.^{4,5} An overview analysis of 22 studies by Prostate Cancer Trial List Collaborative Group revealed only 3% improved overall 5- years survival in favour of combined androgen blockade.⁶ Therefore the efficacy of TAB with gonadal androgen deprivation alone (monotherapy) remains hotly debated.

Advanced prostatic cancer in India is mainly managed by bilateral scrotal orchiectomy. Though combined androgen blockade is advocated, its doubtful efficacy and high cost promoted us to undertake this study in Indian patients comparing bilateral orchiectomy plus placebo v/s bilateral orchiectomy plus flutamide. So the purpose of this study is to compare the effect of total androgen blockade with bilateral orchiectomy, to find out whether addition of flutamide to bilateral orchiectomy is beneficial in improving overall survival in metastatic prostate cancer and to study adverse effect of drug.

METHODS

This 18 months observational study was conducted in the patients coming to the urology unit of department of Surgery, SN Medical College & Hospital Agra, with the symptoms of prostate cancer after taking permission from the Institutional Ethical committee. The procedures were conducted in the ultrasound laboratory, urology operation theatre, departments of Pathology and Medicine.

Newly diagnosed cases of histologically proven adenocarcinoma of prostate with metastases to pelvic lymph node, bone or other sites were included in this study after taking written informed consent.

Patients with progressive fatal illness, terminal stage of disease, Karnofsky's index ≤ 40 , active secondary neoplasm or with prior history of secondary neoplasm and benign hyperplasia of prostate were excluded.

Detailed history of the patient was taken. Digital rectal examination, Trans abdominal and Transrectal ultrasounds, Estimation of serum acid phosphates, Tumor marker PSA estimation, Prostatic biopsy by Transurethral resection of prostate (TURP) and Digital rectal biopsy and Bone scan were done.

Method of Palliation used was bilateral orchiectomy and Anti-androgen flutamide.

Randomization

A total of 12 previously untreated patients with metastatic cancer were entered into a randomization double blind placebo controlled trial of bilateral orchiectomy with or without total androgen blockade (6-receiving flutamide & 6- receiving placebo). The flutamide and placebo therapy was instituted within the 7 days preceding surgery and continued this medication for 18 months with follow-up at every 3rd and 6th month. Weight of the patient, Karnofsky performance, Bladder outlet symptoms, and bone pains, Neurological symptoms, Appetite, Digital Rectal Examination (DRE), Tumour Marker (PSA), Bone scan/x-ray pelvis, Side effects of drug were recorded. Date of stopping current medication/any other treatment received after stopping current medication was noted.

The serum PSA and bone scan was done in each case before the either modes of treatment was started after orchiectomy in both groups first PSA estimation was obtained before treatment at first month and three monthly thereafter. The evaluation of efficacy was based primarily findings of bone scan and the serum PSA value on follow-up. A complete response (CR) was defined as normalization of bone scan and serum PSA returning to normal (4ng/ml). A partial response (PR) was defined as $\geq 50\%$ reduction of metastasis mass in comparison to the initial study or lowering of circulating PSA level fifty percent or more of the initial value. The progression of disease (PD) was defined as development of any new hot spot on bone scan or any increase in previously existing PSA by twenty five percent. Percentage change in PSA value was also calculates each time as compared to the pretreatment value of the two treatment arms.

Statistical analysis was done using SPSS and a p value of <0.05 was considered as statistically significant.

RESULTS

The patients were randomly stratified into two groups. Group I had patients treated with bilateral orchiectomy with placebo and group II had those patients which were treated with bilateral orchiectomy with tablet flutamide. Two patients were aged between 49-59 years, while four were aged between 60-70 and six were between 71-86 years. The incidence of carcinoma prostate increased with the increase in age.

The mean age in group I was 71 and in group II was 66.6. The mean PSA in group I was 46.2 and in group II was 81.0. Fifty percent patients in group I and 66.6% patients in group II had no bony pain as per EORTC Genitourinary group criteria (Table 1).

Table 1: Characteristic of the patients.

Characteristics	B/L Orchiectomy+ plus placebo (group-I)	B/L Orchiectomy plus Flutamide (group-II)
No. of Patients	6	6
Age(Yrs)	49-86	60-76
Mean \pm SD	71 \pm 14.8	66.6 \pm 5.6
PSD (ng/ml)	2.08-127 ng /ml	4.5-147 ng/ml
Mean \pm S.D.	46.3 \pm 44.6	81.08 \pm 46.2
Bone pain (No. %)*		
Nil	3 (50%)	4 (66.6%)
Mild	1 (16.6%)	1 (16.6%)
Moderate	1 (16.6%)	1 (16.6%)
Severe	1 (16.6%)	—

*Criteria adopted by EORTC Genitourinary group

Maximum mean percentage changes in PSA were observed in the first three months after orchiectomy in the two groups. The mean percentage changes were 68% and 73% in group 1st and group 2nd respectively at eighteen months, the difference being statistically insignificant (P value >0.05) (Table 2). The mean PSA changed in the two groups, as shown by the decreasing curve in PSA value in first three months in comparison to pre-treatment value and at eighteen months the curves were parallel to each other showing similar changes in both groups, the difference being statistically insignificant (P value >0.05).

Based on the evaluation of response as defined in the protocol there was no significant difference in response rate between the two treatment groups as shown in Table 4. The overall response rate (CR+PR) was 83.3% in both groups. There was no statistical difference in the two groups (p value >0.05).

Table 2: Percentage changes in PSA in two treatment groups.

Group	Pretreatment PSA ng/ml	1 month	3 month	6 months	9 months	12 months	18 months
I Mean	2-127 (46.27)	1-96 (41)	0.1-55.2 (57)	0.1-50.2 (62)	0.2-72.8 (64)	0.3-70.1 (66)	0.1-65.3 (68)
II Mean	4.5-147 (81.0)	0.5-72 (55)	0.2-60 (60)	0.2-58.2 (64)	0.2-55.1 (66)	0.1-54.1 (68)	0.1-51.7 (73)

Table 3: Mean \pm S.D. of PSA in two treatment groups.

Group	Pretreatment PSA ng/ml	1 month	3 month	6 months	9 months	12 months	18 months
I Mean	2-127	1-96	0.1-55.2	0.1-50.2	0.2-72.8	0.3-70.1	0.1-65.3
S.D.	46.2 \pm 44.6	27.5 \pm 34.8	18.4 \pm 19.5	17.7 \pm 21.3	15.5 \pm 26.6	12.9 \pm 25.6	12.4 \pm 23.3
II Mean	4.5-147	0.5-72	0.2-60	0.2-58.2	0.2-55.1	0.1-54.1	0.1-51.7
S.D.	81.1 \pm 46.32	34.1 \pm 26.4	31.9 \pm 22.8	28.5 \pm 21.3	27.2 \pm 20.2	25.9 \pm 19.7	21.9 \pm 17.9
t =	1.32	0.47	1.10	0.87	1.00	0.98	0.71
p =	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Table 4: Clinical response in two treatment groups.

Response	B/L Orchiectomy + Placebo	B/L Orchiectomy + Flutamide
Complete response (CR)	3 (50%)	2 (33.3%)
Partial response (PR)	2 (33.3%)	3 (50%)
Progressive disease (PD)	1 (16.6%)	1 (16.6%)

In group I (having bilateral orchiectomy + placebo), there was 83.3% survival (5 patients) till 18 months with mortality of 16.6% (1 patient). One death in group I was due to the progressive distant metastasis in liver. While in group II (orchiectomy + flutamide) the survival was 100%. There was no, significant statistical difference in two groups (P value >0.05).

Two patients out of six in the group receiving tablet flutamide experienced hot flushes and diarrhoea. These are the adverse effects of drug, which is 32.6%. Where as in group receiving placebo only one patient out of six had jaundice because of distant liver metastasis. So it is evident that there was a higher incidence of drug reaction in group receiving the course of flutamide therapy.

Table 5: Adverse experience of patients categorized by treatment.

Serious adverse experience	Bilateral orchiectomy (%)	
	Flutamide	Placebo
Total number of patient	6	6
Hot flushes	1 (16.6)	---
Diarrhoea	1 (16.6)	---
Jaundice	---	1 (16.6)

DISCUSSION

The prostate gland is hormone dependent and is controlled by circulatory testosterone, which is synthesized and secreted from the testes up to 90-95%. The ablation of trophic androgen by medical or surgical castration has been the standard therapy for carcinoma of prostate for the last fifty years. The prostatic tumour responds in many ways such as apoptosis, decrease in cell proliferation etc. the androgen especially formed in adrenal gland, is thought to be more important and is still a continuous stimulus of the prostate gland containing receptors for androgen hormone. Bilateral orchiectomy, which is the most effective method for reducing the circulating testosterone, gives the symptomatic relief for up to 80-85%. Such hormonal response in carcinoma prostate depends on the presence of androgen sensitive cells. There are about 20% prostatic carcinomas which are androgen independent. There is no definite way to

detect which patient will respond after orchiectomy and which patient will not respond.

The prostate specific antigen is used as the clinical marker to monitor the disease in surgical and non-surgical treatment. In the present study the maximum percentage of changes in PSA has been recorded in first three month after the orchiectomy. This can be explained up to some extent by the degree of apoptosis and inhibition of cell proliferation both, within the first seven days after orchiectomy.

Labrie and coworkers treated 30 patients with LHRH analogue and a pure antiandrogen flutamide.³ The result was interpreted as dramatic improvement of 96% above the standard treatment especially based on slopes of PSA decrease. They showed remarkable survival in their study. Crawford & Associates showed remarkable longer progression free survival in patients treated with leuprolide and flutamide (35.6 versus 28.3 month; P=0.05).⁷ EORTC phase III prospective trial compared bilateral orchiectomy to orchiectomy plus CPA and DES and it was evident that there was no difference in disease progression as well as survival in all three arms.⁸ Another multicenter randomized trial was done comparing zoladex with zoladex plus flutamide in advanced carcinoma prostate and showed no statistical difference in objective response between two groups.⁹ The response was 67% in zolodex group and was 65% in combination group with no difference in time to treatment failure and time to progression. This is similar to the present study, where 12 patients treated with flutamide and bilateral orchiectomy, also showed 83.3% response rate in both arms with no difference in time to treatment and time to progression.

The best evidence comes from the largest metaanalysis, conducted by the Prostate Cancer Trialists Collaborative Group and based on IPD (8725 patients) from 27 trials.⁶ That analysis detected no difference in overall survival between MAB and castration alone at 2 or 5 years.

Thus a number of randomized clinical trials (RCT) were conducted in the 1990s to investigate the efficacy of CAB with an antiandrogen (nilutamide or flutamide) plus castration; however, there were both positive and negative results for the efficacy of CAB. However, more recently, the efficacy and safety of CAB have been investigated using the antiandrogen bicalutamide.¹⁰ Data from recent trials suggest that CAB with bicalutamide significantly prolongs survival without deteriorating safety and QOL.^{11,12}

One third of patients in the group receiving tablet flutamide experienced hot flushes and diarrhoea in this study. In another study by Ansari, et al.¹³ It is also evident that additional flutamide therapy did not significantly improve the outcome of patients undergoing

bilateral orchiectomy for metastatic carcinoma of the prostate. The usual side effects noted with flutamide were transient nausea, vomiting and diarrhoea.

CONCLUSION

We cannot clearly comment on overall survival because of small sample size, less duration of treatment and follow up of the patients. But it is evident that the addition of antiandrogen like flutamide to orchiectomy has not shown any significant beneficial effect. Hence the use of flutamide to orchiectomy should not be recommended. In addition, in developing country like India where the per-capita income is low, the routine use of flutamide should not be advisable due to its cost effectiveness.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Fincham SM, Hill GB, Hanson J, Wijayasinghe C. Epidemiology of prostatic cancer: a case-control study. *Prostate*. 1990;17(3):189-206.
2. Huggins C, Hodges CV: Studies on prostate cancer: The effects of castraxton on advanced carcinoma of the prostate gland. *Arch Surg*. 1941;43:09.
3. Labrie F, Dupont A, Belanger A. New approaches in the treatment of prostate cancer: Complete instead of partial withdrawal of androgens. *Prostate*. 1983;4:579-94.
4. Schroder FH Lock TMTW, Chadha DR. Metastatic cancer of the prostate managed with busereline plus cyproterone acetate. *J. Urol*. 1987;137:912-8.
5. Iversen P, Christensen MG, Friis E. A phase iii trial of Zoladex and flutamide versus orchiectomy in the treatment of patients with advanced carcinoma of the prostate. *Cancer*. 1990;66:1058-66.
6. Prostate cancer trial list Collaborative group: Maximal androgen blockade in advance prostate cancer: an over view of 22 randomized trials with 3289 deaths in 5710 patients. *Lancet*. 1995;346-269.
7. Crawford ED, Eisenberger MA, MeLeod DG. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med*. 1989;321-419.
8. Denis LJ. Goserelin acetate and flutamide V/s bilateral orchiectomy: a phase 3 EORTC trial (30853). *Urology*. 1993;42:119.
9. Keuppens F, Denis L, Smith P, Sylvester R, Ongena P and the EORTC GU Group: Zoladex and flutamide versus bilateral orchiectomy. A randomized phase III EORTC 30853 study cancer. 1990;66:1045-57.
10. Akaza H. Combined androgen blockade for prostate cancer: Review of efficacy, safety and cost-effectiveness. *Cancer Sci*. 2011;102:51-6.
11. Hinotsu S, Akaza H, Usami M. Study Group for the Combined Androgen Blockade Therapy of Prostate Cancer. Combined androgen blockade (CAB) with bicalutamide and a luteinising hormone-releasing hormone agonist Japanese patient with advanced prostate cancer. Long-term follow-up reporting overall and cause-specific survival. 1st European Multidisciplinary Meeting on Urological Cancers: Embracing Excellence in Prostate and Kidney Cancer, Barcelona, Spain. 2007:2-4.
12. Akaza H, Hinotsu S, Usami M. Study Group for the Combined Androgen Blockade Therapy of Prostate Cancer Combined androgen blockade with bicalutamide for advanced prostate cancer: long-term follow-up of a phase 3, double-blind, randomized study for survival. *Cancer*. 2009;115:3437-45.
13. Ansari MS, Gupta NP, Hemal AK, Dogra PN, Seth A. Orchiectomy versus combined androgen blockade in the management of advanced carcinoma prostate. *Indian J Urol*. 2001;18:52-6.

Cite this article as: Rajesh, Nigam DK. Bilateral orchiectomy versus total androgen blockade in the management of metastatic cancer prostate. *Int Surg J* 2016;3:841-5.