Original Article

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Comparative Study Evaluating Safety and Efficacy of Bicalutamide (150 mg) Monotherapy versus Orchidectomy and Bicalutamide (50 mg) in the Treatment of Locally Advanced/Metastatic Prostate Cancer

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Abstract

Background: Prostate cancer is one of the leading causes of death in men. The approach to prostate cancer diagnosis and treatment is changing rapidly across the spectrum of the disease. We studied, locally advanced and metastatic cancer prostate in our study. Suppressing both testicular and adrenal androgen known as combined androgen blockade (CAB), allows for a better initial and longer response compared with those methods that inhibit the production of only testicular androgen. We assessed the safety and efficacy of two methods of CAB for locally advanced/metastatic Ca prostate, i.e., orchidectomy with bicalutamide 50 mg versus bicalutamide 150 mg daily (without orchidectomy).

Materials and Methods: The present study included 50 prospective patients of locally advanced or metastatic Ca prostate. A detailed history regarding symptoms of Ca prostate, complete physical examination, digital rectal exam (DRE), and baseline investigations that included hemogram, urine R/E, urine C/S, liver function tests, renal function tests, prostate-specific antigen level, radiological included whole body X-rays, transrectal ultrasound/imaging computed tomography scan, and bone scan were done. Sextant prostate biopsy - Gleason grading and other metastatic evaluation were carried out before starting of the treatment. A comparative analysis of the effect of 2 different treatments was assessed by eastern cooperative oncology (Group) performance grading criteria, symptoms-general, urinary and side effects of medication, morbidity, and progress of disease.

Results: We observed that monotherapy (150 mg) and surgical castration + bicalutamide (50 mg) in men with locally advanced prostate cancer offers better tolerability and higher health-related quality of life.

Conclusion: Anti-androgen therapy in combination with surgical castration is given to enhance survival and to maintain or improve the quality of life of patients with advanced prostate cancer. Bicalutamide appears to have a more favorable tolerability profile than either therapy on the basis of current evidence.

Key words: Complete androgen blockage, Bicalutamide, Monotherapy in Ca prostate

INTRODUCTION

The prostate gland is an exocrine organ weighing 20-25 g, located deep in the pelvic between the bladder and the external urinary sphincter in male anterior to the rectum and behind symphysis pubis. Prostate cancer is one of the leading causes of death in men. The incidence of prostate cancer in India is 1.4 to 7.9/100000 populations.[1] The approach to the prostatic cancer diagnosis and treatment is changing rapidly across the spectrum of the diseases.

The traditional treatment for locally advanced and metastatic adenocarcinoma prostate has been bilateral orchidectomy. Over the past 50 years, numerous medications have been developed and tested that achieve a medical castration

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with no overall change in the survival. It is well known that most of the prostatic carcinomas are hormone dependent and that approximately 70-80% of man with metastatic Ca prostate respond to a various form of androgen deprivation. Although testosterone is the major circulating androgen produced by testicles, the adrenal glands secrete the androgen dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione. Suppressing both testicular and adrenal androgen known as combined androgen blockade (CAB), allows for a better initial and longer response compared with those methods that inhibit the production of only testicular androgen. Complete androgen blockade can be achieved by combining an anti-androgen with the use of a luteinizing hormone-releasing hormone agonist or orchidectomy. Non-steroidal anti-androgen such as bicalutamide in higher doses offers an effective alternative to CAB with potential quality of life benefits.

Aims and Objectives

1. To compare the safety and efficacy of bicalutamide - 150 mg monotherapy versus orchidectomy and bicalutamide - 50 mg.
2. To monitor the effect of treatment and progression of disease.
3. To study the complications and side effects of the disease.
4. To formulate our recommendation for the treatment of locally advanced/metastatic Ca prostate based on our observation.

MATERIALS AND METHODS

The present study included 50 prospective patients of locally advanced or metastatic Ca prostate.

The following inclusion and exclusion criteria were applied.

Inclusion Criteria

1. Locally advanced/metastatic prostate cancer patients diagnosed/confirmed histologically/cytologically.

Exclusion Criteria

1. The presence of any other cancer of organs or any other concomitant disease that would interfere with the treatment of/or patient compliance.
2. Any severe renal or hepatic dysfunction - serum creatinine > 2.5 mg/dl, serum bilirubin, and/or serum transaminases > 50% of upper normal limits
3. Patient's performance status of 3-4 (as per Eastern Cooperative Oncology Group [ECOG] criteria).

Methods

1. A detailed history regarding symptoms of Ca prostate, complete physical examination, digital rectal exam (DRE), and baseline investigations that included hemogram, urine R/E, urine C/S, liver function tests (LFT), renal function tests, prostate-specific antigen (PSA) level, radiological included whole body X-rays, transrectal ultrasound (TRUS)/imaging computed tomography (CT) scan, and bone scan were done. Sextant prostate biopsy - Gleason grading and other metastatic evaluation were carried out before starting of the treatment.
2. An informed and written consent was taken before the start of the treatment.
3. Proven cases of Ca prostate with locally advanced or metastatic disease were subjected to two different Groups of 25 patients in each group.
4. Group A: Bicalutamide 150 mg as monotherapy. Group B: Those who underwent orchidectomy and bicalutamide 50 mg being added. Bicalutamide was started daily with or without meal on the same hour of the day.
5. Serum PSA level estimation was done.
6. A comparative analysis of the effect of 2 different treatments was assessed by ECOG performance grading criteria, symptoms-general, urinary and side effects of medication, morbidity and progress of disease.
7. All these biochemical investigations were done on the 4^{th}, 5^{th}, 6^{th}, 9^{th}, 12^{th}, 15^{th}, and 18^{th} months after the start of the treatment.
8. TRUS/TRUS Guided Biopsy: TRUS was done at the start and 12 months of treatment comparing the volume of prostate.

10 X-ray of the whole body and CT scan of abdomen and pelvis were done at the start and 12 months of treatment to assess invasion of periprostatic tissue, lymph node involvement, and metastasis in another organ.

11 Bone scan was done at the start and 12 months of treatment.

12 Follow-up: All Patients were followed with all hematological and biochemical parameters on the 4^{th}, 5^{th}, 6^{th}, 9^{th}, 12^{th}, 15^{th}, and 18^{th} months after the start of the treatment. They were evaluated by asking about improvement in their performance as compared to previous grade (as per guidelines for ECOG performance grading) and simultaneously evaluated clinically also. All Patients were following up for 18 months. None of the patients were lost to follow-up since all of them being Ex-service Man of the Army were covered under Ex-Serviceman Contributory Health Scheme and reported regularly for follow-up, and there was no mortality during the study.

13 Data-analysis: Paired *t*-test and Chi-square test were applied to derive at the value of significance, *P* value.

RESULTS

In the present study, the range of age of patients was 59-82 years with mean of 67.4 and 70.28 in Group A ($n = 25$) and Group B ($n = 25$), respectively. The mean age of patients was 67.4 years in Group A and 70.28 years in Group B with a range of 59-82 years (Table 1).

Table 2 depicts the history observed in Group A and Group B in 0 month and 18 months, respectively.

Decrease in the grade of DRE in Group A was from mean of 3.12-1.92 and in Group B was from 3.08 to 1.68 (Table 3).

In Group A, PSA falls from mean of 44.48-13.796 after 18 months of treatment. In Group B, PSA falls from mean of 57.94-3.4804 after 18 months of treatment. Decrease in volume of the prostate gland in Group A was from mean of 64.88 to 35.52 g and in Group B was 69.48-40.08 g. No change in hematological and biochemical parameters occurred after 18 months (Table 4).

Table 5 depicts initial total workup in both the groups; Group A and Group B.

In Groups A and B, each having 25 patients all were in Grade 2 of ECOG scale initially. Out of 36% of cases in Group A and in Group B, 32% of cases reached to Grade 0 of ECOG performance grading; 44% of Group A and 64% of Group B in Grade 1; 12% of Group A and 4% of Group B in Grade 2; and 4% of Group A deteriorate to Grade 4 after 18 months of treatment (Table 6).

Breast pain and tenderness in 40% of cases in Group A only and no patient with breast pain in Group B. Gynecomastia occurred in 28% of cases in Group A and 4% of cases in Group B. Hot flashes in 8% of cases in Group A and 32% of patients with Group B (Table 7).

The follow-up period was 18 months.

We have compared each parameter at the start and 18 months of commencement of treatment. We discontinued the treatment in Group A after 18 months in 28% of cases because of severe breast pain and gynecomastia and offered them orchidectomy and low doses of bicalutamide (50 mg).

Table 1: Age range

Age	Minimum years	Maximum years	Mean
Group A (*n*=25)	59	78	67.4
Group B (*n*=25)	57	82	70.28

Table 2: History

Symptoms	Group A		Group B	
	0 month	18 months	0 month	18 months
Hematuria	6	1	5	Nil
Bladder outlet obstruction	12	2	14	3
Urinary tract infection	7	1	5	Nil
Bony pain	4	1	3	Nil
Lower extremity edema	Nil	Nil	Nil	Nil
Paraplegia (spinal cord compression)	Nil	Nil	Nil	Nil

Table 3: Physical examination: DRE-decrease in grades

Group	Baseline		18 months	
	A	B	A	B
Minimum (grade)	2	2	1	1
Maximum	4	4	3	3
Mean	3.12	3.08	1.92	1.68

Table 4: Investigation

Investigations	Group A		Group B	
	0 month	12 month	0 month	12 month
Mean hypoechoic lesion by TRUS	1.92	1.25	1.72	1.0
Periprostatic tissue involvement	25	12	25	14
Lymph node involvement	07	03	09	04
CT scan abdomen and pelvis: Distant metastasis	03	03	04	04
Bone scan showing bony meats	05	03	06	03
Mean PSA	44.48	57.94	13.7960	3.4804
Mean tumor size in grams by TRUS	64.88	69.48	35.52	40.08

TRUS: Transrectal ultrasound, CT: Computer tomography, PSA: Prostate-specific antigen

Table 5: After initial total workup we found

Group	Locally advanced	Metastatic	Total
A	15	10	25
B	13	12	25

Table 6: ECOG grading after 18 months of treatment

Grade	Group A		Group B	
	No. of patients	%	No. of patients	%
0	12	48	15	60
1	7	28	9	36
2	5	20	1	4
3	0	0	0	0
4	1	4	0	0
Total	25	100	25	100

ECOG: Eastern Cooperative Oncology Group

Table 7: Adverse effects

Complications	No. of patients in Group A (*n*=25)	%	No. of patients in Group B (*n*=25)	%
Breast pain	10	40	Nil	Nil
Gynecomastia	7	28	1	4
Hot flushes	2	8	8	32
GIT disturbances	Nil	Nil	Nil	Nil
Cardiovascular	Nil	Nil	Nil	Nil
Respiratory	Nil	Nil	Nil	Nil
CNS	Nil	Nil	Nil	Nil
Skin	Nil	Nil	Nil	Nil

CNS: Central nervous system, GIT: Gastrointestinal

DISCUSSION

The methods for treatment of locally advanced and metastatic carcinoma prostate have increased manifold over the last decade or so, especially when it has been observed that it can be offered without orchidectomy.

This is a prospective study which was aimed at evaluating the safety and efficacy of bicalutamide 150 mg monotherapy versus orchidectomy and bicalutamide 50 mg in the treatment of locally advanced/metastatic prostate cancer.

A prospective study done by Iversen *et al.* compared monotherapy 150 mg with castration on patients with non-metastatic locally advanced prostate cancer, minimal follow-up of 6.3 years, follow-up were not significantly different with bicalutamide or castration in men with locally advanced prostate cancer. There was no significant difference between bicalutamide and castration for overall survival. With respect to health-related quality of life factors - health-related quality of life (HR-QOL), bicalutamide recipients had a significant greater sexual interest ($P = 0.029$) and physical capacity, $P = 0.049$, at 12 months than men who had been castrated. No other significant differences were seen in any of the other HR-QOL parameters (emotional well-being, vitality, social function, pain activity limitation, bed disability, and overall health).[2]

In our study, there was significant fall in PSA value after the start of treatment in both groups separately but to compare between two groups were insignificant. Newling *et al.* found that only moderate correlation between the effect of bicalutamide on PSA progression and objective overall survival.[3]

Iversen *et al.* data from the bicalutamide (Casodex) early cancer program - analysis of combined data by stage at median follow-up showed that the risk of objective progression and PSA doubling was reduced with bicalutamide, irrespective of lymph node status.[4]

In our study, there was 20-60% decrease in volume of prostate gland compares to study done by Bosch *et al.* in 1989; Matzkin *et al.* in 1990; and Whittington *et al.*, 1999 in these studies there was 30% reduction in the volume of prostate.

In our study, hot flashes were present in 8% of cases in Group A and 32% of cases on Group B and study by Iversen *et al.* and Kolvenbag *et al.* showed that hot flashes occurred in 5-28% of cases with bicalutamide 150 mg monotherapy and 24-76% of cases with combined therapy.

Breast tenderness in 40% of cases in Group A and none in Group B. Study by Iversen *et al.* and Kolvenbag *et al.* showed that breast pain and tenderness in 49% of cases in Group A and 4% of cases with combined therapy.

Gynecomastia in 28% of cases in Group A and 4% of cases in Group B which was within the range studied done by Iversen *et al.* and Kolvenbag *et al.* showed 16-60% in bicalutamide 150 mg monotherapy and 6% of cases with combined therapy.[5,6]

Testosterone stimulates renal erythropoietin production, and castration is accompanied by a decrease in hemoglobin of 1-3 g/dl. If anemia becomes symptomatic, it can be effectively treated with recombinant erythropoietin and studied by Holzbeierlein *et al.* However, in our study, we have not found patients with symptomatic anemia.[4,7]

In our study, there was no abnormality found in LFT, but the incidence of abnormal LFT reported as adverse events in Early Prostate Cancer program with bicalutamide monotherapy was 3.1%.[8]

We requested for complete radiographic evaluation. Bone scan of patients to look for metastatic disease at baseline and 12 months of treatment. The bone scan found to have very sensitive methods for assessment of axial skeletons but have a very high level of false positives undergoing staging evaluation, detecting not only metastatic disease but also healing fractures, arthritis, bony infections, and magnitude of other inflammatory conditions. We confirmed the suspicious lesion on the bone scan by plain bone films. Chest radiograph is necessary in initial staging, as 6% of patients may have pulmonary metastasis at the time of presentation according to Lindell *et al.* However, in our study, we have not found any patients with pulmonary metastasis.[9]

We discontinued the treatment of Group A because of severe breast tenderness and gynecomastia in 7 patients (28%) of patients and offered them orchidectomy and low doses of bicalutamide after 18 months of follow-up.

Studies by McLeod *et al.* in which they discontinued the treatment in 29.3%.

This is a prospective study conducted on 50 patients.

The most common adverse events associated with bicalutamide monotherapy were breast pain and gynecomastia.

Bicalutamide 50 mg is an effective, oral once-daily, non-steroidal anti-androgen, available for the use in combination therapy.

The problem of bicalutamide monotherapy lies mainly in its more unfavorable side effects pattern but the advantage of reversibility of these side effects with discontinuation of treatment.

The cost of combined therapy with bicalutamide per months of survival benefits is reasonable and compared with other cancer therapies.

Combination therapy in an important option in the treatment of patients with advanced prostate cancer.

The palliation of prostate cancer by castration was a key clinical advanced in the 20th century oncology. While the androgen deprivation therapy by bicalutamide on symptomatic prostate cancer is dramatic. When androgen deprivation therapy is undertaken, impact on QOL can be minimized through prevention or early identification of treatment side effects.

Hence, when treatment option being offered bicalutamide as combined therapy or monotherapy should be considered as an alternative to other available hormonal therapies.

The debate concerning the benefits of combination therapy will continue; nevertheless, this approach is an important option in the treatment of patients with advanced disease, as highlighted in many clinical studies.

Anti-androgen therapy in combination with surgical castration is given to enhance survival and to maintain or improve the quality of life of patients with advanced prostate cancer.

CONCLUSION

In our study, we conclude that compared to Monotherapy (150 mg) and surgical castration + bicalutamide (50 mg) in men with locally advanced prostate cancer offers better tolerability and higher HR-QOL. Bicalutamide appears to have a more favorable tolerability profile than either therapy on the basis of current evidence.

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