Original Article

موضوع أصيل

IS COMBINED ANDROGEN BLOCKADE BY SURGICAL CASTRATION AND FLUTAMIDE NECESSARY AS AN INITIAL THERAPY FOR PATIENTS WITH ADVANCED PROSTATE CANCER?

ضرورة الحصر الأندروجيني المشترك بتطبيق الإخصاء الجراحي

واستعمال عقار flutamide كعلاج أولي عند مرضى سرطان البروستات المتقدم

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ملخص البحث

هدف البحث: دراسة كفاءة الإخصاء الجراحي بواسطة استئصال الخصيتين فقط أو استئصال الخصيتين مع استعمال عقار flutamide كعلاجٍ أولي عند مرضى سرطان البروستات المتقدم.

طرق البحث: تم إجراء دراسة عشوائية سريرية تضمنت 60 مريضاً من المصابين بسرطان البروستات المتقدم خلال الفترة بين عامي 2012 و2017. أجري الإخصاء الجراحي لجميع المرضى، تم بعد ذلك توزيع المرضى عشوائياً إلى مجموعتين: المجموعة الأولى ضمت المرضى الذين خضعوا للإخصاء الجراحي فقط، بينما ضمت المجموعة الثانية المرضى الذين طبق لديهم علاج باستخدام flutamide بالإضافة للإخصاء الجراحي. تمت متابعة المرضى على مدى السنتين التاليتين مع مراقبة معدلات الاستجابة والبقاء على قيد الحياة.

النتائج: أظهرت الدراسة أن المعدل المئوي للتغيير في قيمة PSA في كلتا المجموعتين من المرضى كان متقارباً، كما أن المرضى في كلتا المجموعتين لم يظهروا أي اختلافٍ هام إحصائياً بالنسبة لاستجابتهم للعلاج بعد مرور سنتين من إجراء الإخصاء الجراحي.

الاستنتاجات: إن الاستخدام الأولي لعقار flutamide عند مرضى سرطان البروستات المتقدم بعد إجراء الإخصاء الجراحي لا يحقق أية فائدة إضافية هامة أو تأثير على معدل التغيير في قيم PSA الملاحظة عند هؤلاء المرضى.

ABSTRACT

Objective: *Prostate cancer incidence and mortality vary widely among countries. Surgical castration by orchidectomy with or without hormonal therapy is one approach for patients presenting with advanced disease. The aim of this work was to study the efficacy of surgical castration by orchidectomy alone versus orchidectomy with flutamide, as an initial treatment for patients presenting with advanced carcinoma of prostate.*

Methods: *This randomized clinical trial included 60 patients presenting with advanced prostatic cancer between 2012 to 2017. Surgical castration by orchidectomy was done for all patients followed by randomizing them into two groups; group I with surgical castration only and group II with castration plus flutamide therapy. The patients were followed up for their response rates and survival for the next two years following castration.*

Results: *The mean percent of change in the values of PSA in the two arms of the study was close. The patients in the two arms of the trial showed no significant*

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difference regarding their response rate at the end of first two years following orchidectomy.

Conclusions: *Initial use of flutamide following orchidectomy seems to add no significant benefit in regard to changes in PSA and the survival in these patients.*

INTRODUCTION

The incidence of prostatic cancer and its mortality diverge greatly among countries and world regions and are the highest in African American men. Prostatic cancer in USA is known to be the most prevalent malignant tumor in males, and the second major cause of cancer-associated deaths. Testing for PSA has prompted a remarkable downward peregrination in stage and age at time of diagnosis, this is both clinical and pathological. It is well known that genetic prerdispostion and environmental factors play importantly in the rise and progress of prostatic cancer.[1-3]

Labrie et al[4] demonstrated excellent outcomes with the use of CAB in several non randomized trials, and since that the interest concerning endocrine treatment for prostatic cancer has been pointed towards CAB. The imposing results obtained by Labrie et al drived many urologists to produce CAB by adding anti-androgens to eliminate the nourishing effect of adrenal androgens for prostatic cancer. However, other authors never attained the excellent results obtained by Labrie. The results of subsequent studies were inconsistent making complete androgen blockade a question to be resolved.[5,6]

This study aims to answer the question of need to the use of anti-androgen (flutamide) together with orchidectomy to improve treatment outcomes of advanced prostatic cancer in Basrah Urology Center.

METHODS

This randomized clinical trial included 60 patients diagnosed with advanced prostatic cancer who attended Basrah Teaching Hospital from October 2012 to October 2017. Recruitment of patients to the study was done after preparing the center for the appropriate planned therapies and their requirements. The study was conducted in accordance with good clinical practice, and the 1964 Declaration of Helsinki, including the most recent amendments (Edinburgh, Scotland). The trial obtained the ethical approval from the Researches Ethical Committee Board at Basrah College of Medicine.

Patients who were eligible for the current study had been diagnosed histologically with prostate cancer, beside the presence of distant metastasis or locally advanced disease. A written consent from the patients was obtained before recruitment to the study.

Among these patients, fifteen were diagnosed with prostatic cancer after they had TURP for symptomatic prostatic enlargement with or without abnormally high PSA reading, while forty five patients were diagnosed on basis of multiple core prostatic biopsies for evaluation of high PSA values.

Serum testosterone was measured for all patients before treatment and it was within normal range for all of them. Patients who underwent TURP had their PSA assessed before surgery. Seven of them showed normal PSA values and eight showed elevated PSA values. All 60 patients were thoroughly evaluated by detailed physical examination and laboratory and imaging investigations.

Laboratory tests included complete blood count and evaluating renal function tests including blood urea nitrogen and serum creatinine levels. Imaging studies that were done included radiology of lumbar spines and sonography examination of the abdomen. Computerized tomography scanning (CT) was performed for patients with suspected secondary deposits, like patients with abnormal sonography findings or abnormal findings of the spines on radiology. Secondary deposits were seen in the spines of 20 patients, while 15 patients presented with evidence of visceral metastases involving the lungs and the liver. Twenty five patients presented with evidence of locally advanced disease.

All patients were prepared for bilateral orchidectomy after giving formal consent. The orchidectomy was done via scrotal approach. Following surgery; the

patients were stratified randomly into two categories. Category I included patients who underwent bilateral orchidectomy alone (30 patients), and Category II those treated with bilateral orchidectomy followed by flutamide (30 patients).

In both groups, following orchidectomy, the initial assessment of PSA serum testosterone was carried out after the first month following surgery and three monthly later on. The definition of success was based on findings of bone radiology and the serum PSA and testosterone values on follow-up.

In this study, the definition of a complete response (CR) included regression of bone secondaries on X-ray, and return of serum PSA to normal (cut-off point <4 ng/ml), and serum level of testosterone (<50 ng/dl, castration level). On the other hand, a partial response (PR) was needed to be adopted and was defined as a reduction in the burden of metastasis more than 50% of the initial findings, or decrease in the serum levels of PSA and testosterone (≥50%) of the initial values. A third response (progressive disease, PD) was defined as a rise of any new lesion on bone radiology, or any rise in PSA or serum testosterone levels by 25%. In both groups, percentage change in serum levels of PSA and testosterone was measured every time, and compared to the pretreatment value to establish the efficacy of study arms.

Unpaired Student t test was used to perform between arm analyses. A two-tailed p-value <0.05 was adopted statistically significant.

The characteristics of the patients are shown in Table 1. The 60 subjects enrolled in the study were considered the safety dataset and underwent the analysis. For the first group (which included 30 subjects), one patient discontinued the follow-up and did not complete the primary endpoint. Three patients were followed-up initially, but were lost for follow-up and did not complete the secondary end point, one of them was lost for follow-up after 6 months following surgery, and two were lost for follow-up after 10 months and 12 months, respectively. These patients developed cardiovascular problems, so only 26 patients (43.3%) were analyzed. For the second group (which included 30 subjects), three patients discontinued follow-up, and two were followed-up initially but lost for follow-up 7 months and 9 months, respectively. So only 25 patients (41.6%) were analyzed. The trial flow chart is seen in Figure 1.

After castration by orchidectomy, the mean of change in the values of PSA was maximally noticed in the first three months following surgery (Table 2), which was 5 for group I and 5.2 for group II.

For the patients who were followed up for the next two years and remained castration- responsive, the mean percent of change in the values of PSA in the two arms of the study was 65% and 62% respectively (Table 3). This was statistically insignificant (p-value =0.95).

Characteristics	Orchidectomy alone (Group I)		Orchidectomy with Flutamide (Group II)	
Number of patients	30		30	
Age (years)	56-75		55-75	
PSA (ng/ml)	10-100		8-80	
Bone pain	Number	Percentage	Number	Percentage
Nil	12	40%	16	53.3%
Mild	9	30%	5	16.6%
Moderate	4	13.3%	5	16.6%
Severe	5	16.6%	4	13.3%
Intractable	0	0%	0	0%

Table 1. Characteristics of the patients (pre-treatment).

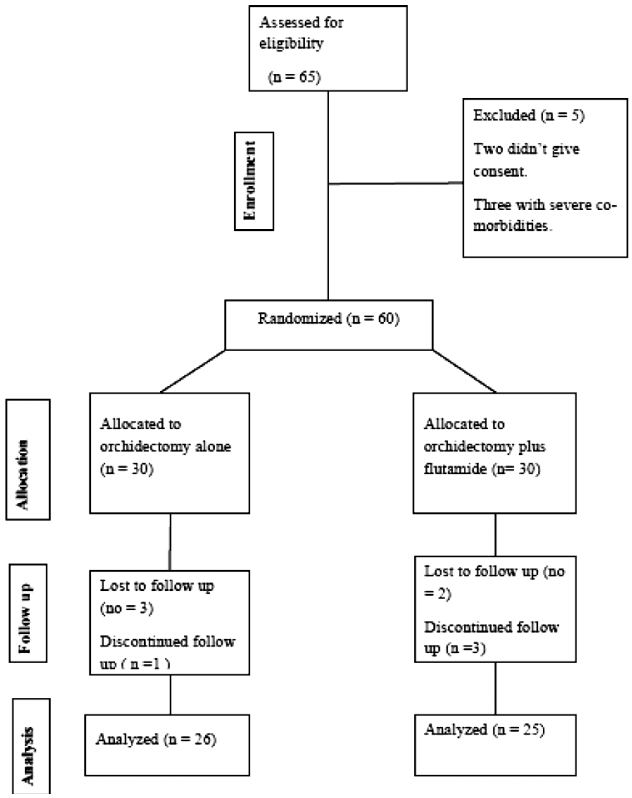

Figure 1. Consolidated standards of reporting trials flow chart for the trial.

For both arms of the study, the mean percent of change in the values of testosterone two years following surgery was 64% and 62% respectively, (Table 4). Again this suggested insignificant difference (p-value =0.92).

According to the protocols of response defined by the current study, the two arms of the trial showed no significant difference regarding their response rate at the end of first two years following orchidectomy. For group I, five patients (19.23%) showed complete response, 17 patients (65.38%) showed partial response, while 4 patients (15.38%) showed progressive disease. On the other hand, for group II, 4 (16%) showed complete response, 16 (64%) showed partial response and 5 patients (24%) showed progressive disease, (Table 5). This was insignificant difference in the response rate between the two groups (p-value >0.05).

DISCUSSION

A well known fact is that testosterone is the main fuel that nourishes prostatic cancer. This was stated by Charles Huggins in 1941. The testes synthesize and secret 90-95% of the circulating testosterone. Androgen deprivation therapy (ADT) is the golden standard for treating advanced cancer of prostate. Elimination of androgen can be achieved by medical or surgical castration.

ADT is known to induce ablation of androgen which promotes apoptotic cell death.[7] The initial therapeutic effect of (ADT) in advanced prostate cancer is caused by apoptotic depletion of hormone-dependent cancer

Group	Pre-treatment PSA (ng/ml) range and (mean)	1 month	3 months	6 months	12 months	18 months	24 months	p-value
I	10-100 (18.6)	7-20 (7.5)	4-13 (5)	3-16 (5.7)	4.5-14 (6.1)	6.5-15 (7)	6-16 (6.5)	>0.05
II	8-80 (18.2)	6-21 (7.4)	3.8-13.5 (5.2)	4.5-13 (5.6)	4-12 (5.9)	5-13 (7.2)	5.2-15 (6.9)	>0.05

Table 2. Changes in the PSA level in the two groups before and after therapy.

Group		1 month	3 months	6 months	12 months	18 months	24 months	p-value
Mean percentage change	I	59.7%	73.1%	69.3%	67.2%	62.3%	65%	>0.05
	II	59.3%	71.4%	69.2%	67.5%	60.4%	62%	>0.05

Table 3. Mean percentage change in PSA level in the two treatment groups after therapy.

Group		1 month	3 months	6 months	12 months	18 months	24 months
Mean percentage change	I	57.7%	71.1%	68.4%	66.2%	61.3%	64%
	II	57.3%	70.4%	68.2%	66.3%	60.8%	62%

Table 4. Mean percentage change in testosterone level in the two treatment groups after therapy.

Group	Pre-treatment PSA (ng/ml) range and (mean)	1 month	3 months	6 months	12 months	18 months	24 months	p-value
I	10-100 (18.6)	7-20 (7.5)	4-13 (5)	3-16 (5.7)	4.5-14 (6.1)	6.5-15 (7)	6-16 (6.5)	>0.05
II	8-80 (18.2)	6-21 (7.4)	3.8-13.5 (5.2)	4.5-13 (5.6)	4-12 (5.9)	5-13 (7.2)	5.2-15 (6.9)	>0.05

Table 5. Clinical response in the two treatment groups after therapy.

cells.[8] The adrenal cortical androgens may play a very important role in continuing stimulation for the prostatic cancer.[9]

Surgical castration by orchidectomy can produce relieve of symptoms of advanced prostate cancer, like bone pain for up to 70-80% of cases.[10,11] Castration-resistant prostate cancer incidence is estimated to be about 20%.[12]

Flutamide is a non-steroidal anti-androgen that achieves its effect by blocking the uptake and the binding of dihydro-testosterone to the hormone-sensitive cells, thereby interfering with androgen action. Flutamide side effects are gynecomastia and mild diarrhea when used as monotherapy, and loss of libido, impotence, hot flashes, nausea and vomiting, diarrhea and gynecomastia when used in combination with an LHRH-agonist.

Inactivation of some oncogens (for example P53) is thought to block the apoptotic effect that is induced by castration on prostatic cancer cells.[13] This may explain why some people may not respond to orchidectomy to control their disease status. Some trials suggested that expression of oncoproteins like P53, C-myc and Bcl-2 may predict the response to orchidectomy and being in a castration-responsive status.[14,15] Monitoring the progress of prostate cancer whether treated surgically or not is done by serial assessment of PSA. It was shown in some studies that a marked increase in the process of apoptosis in normal prostatic tissues was noticed after 7 days following castration.[15] In the current study, PSA changes after orchidectomy were recorded and the maximum percent of changes in PSA was noticed within the first three months following orchidectomy. The explanation for this can be attributed to the marked level of apoptosis, which is at maximum degree within the early period following orchidectomy.[15]

In the study of Labrie et al, the response rate and long term survival was 96% in patients with advanced prostatic cancer treated by (ADT).[4] However, similar excellent results were not achieved by other studies. Many randomized trials showed better outcomes with (CAB).[16,17]

A study carried out in United States of America (National Cancer Institute) compared the use of LHRH agonist with flutamide to that of LHRH agonist with placebo. The outcome of that multicentric study showed that the combination of LHRH agonist with flutamide was superior to the use of LHRH agonist

alone in controlling low volume advanced cancer of the prostate.[18]

Previous studies showed major advantages of complete androgen blockade over orchidectomy. After that more controlled trials did not show any significant advantage of complete androgen blockade compared to orchidectomy alone. Again previous trials suggested that complete blockage of androgen was effective mainly in patients having good performance and with low volume of disease.[19,20]

Furthermore, an EORTC phase III prospective trial that compared orchidectomy to orchidectomy with diethyl stillbestrol and cyproterone acetate showed that there was no big difference in progression and survival rates in the three arms of the study.[20]

In a multicenteric randomized trial testing the use of cyproterone acetate to buserline did not alter the treatment outcomes compared to orchidectomy alone.[21]

In another multicentre, randomized trial that compared treatment with zoladex alone to treatment with zoladex and flutamide for patients with advanced cancer, there was no big differences in the treatment response between the first group which was 67% and the second group which was 65%. In addition, there was no difference in time before failure of treatment and progression of disease between the two arms of the study.[22]

The Agency for Health Care Policy and Research recently published the results of a meta-analytic study including 27 published studies evaluating the use of (CAB). This study showed no difference in 2-year survival rates in patients who underwent orchidectomy alone versus those who underwent combined hormonal blocked. Among these 27 studies, only 10 reported 5-year survival rates, and showed a minimal difference in the survival rate in favor of (CAB).[23]

The additional use of an anti-androgen (like flutamide) following surgical castration as a first line treatment in patients diagnosed with advanced prostatic cancer seems to affect the patients' quality of life because of the high probability of side effects.[24]

CONCLUSIONS

Surgical castration of patients with advanced carcinoma of prostate can yield a maximum decrease of PSA in the first three months after surgery. Initial additional use of an anti-androgen (like flutamide) to orchidectomy does not seem to add any significant benefit in regard to changes in PSA and the survival in these patients. Larger randomized clinical trials are needed to help the clinicians in deciding the appropriate treatment in order to offer a cost-effective management of patients with advanced prostate cancer, and to minimize possible side effects of the anti-androgens, beside the possibility of keeping them as a second option for patient who develop castration resistance.

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