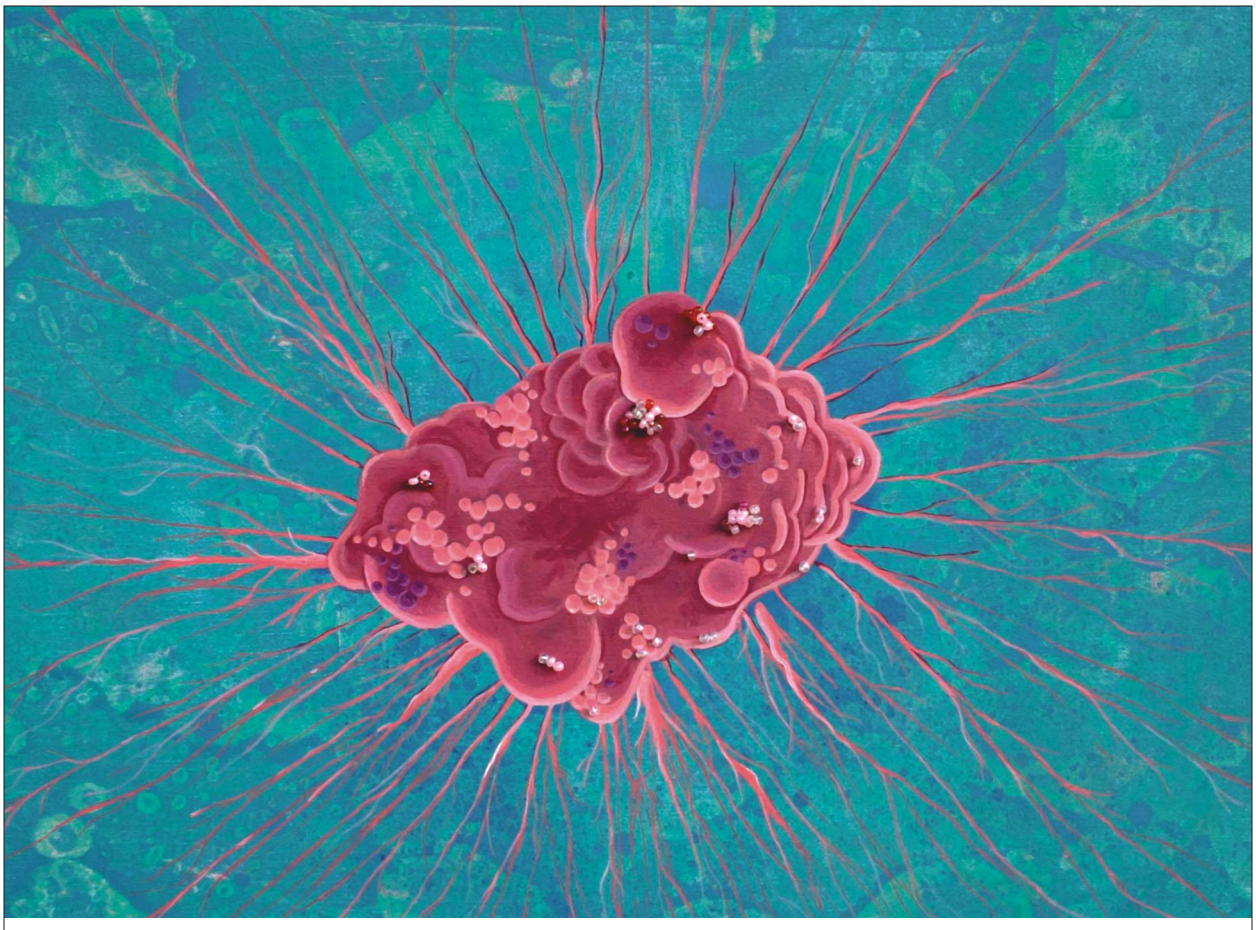

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Research Article
Efficacy of Metformin in Treatment of Patients with Advanced Prostate Cancer: Single-arm Phase II Clinical Study

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Abstract

Background and Objective: The anti-neoplastic activities of metformin were investigated in many pre-clinical and clinical studies. In this study, metformin which is familiar oral drug, cheap and available in all places was used to evaluate its efficacy in Egyptian patients with advanced prostate cancer. **Materials and Methods:** Twenty six patients with advanced prostate cancer either treatment naïve or previously treated were subjected to metformin therapy. Metformin was administered as glucophage1000 mg twice daily concomitantly with standard of care treatment continuously till disease progression, drug toxicity or patient refusal. **Results:** The median age of studied patients was 65 years, range 59-75 with median body mass index 24.75 range 17-40, 18 cases had ECOG PS of one and the remaining cases were ECOG 2. Out of 26 patients, 17 were treatment naïve while 9 of them were subjected to previous SOC treatment. The overall response (CR, PR) was 53.8%, no response (SD, PD) represented 46.2% and the median time to tumor progression (TTP) was 18 weeks but it was significantly different in previously treated cases and treatment naive cases, in which median TTP in previously treated case was 8 weeks compared to 32 weeks in treatment naïve cases [p<0.001, HR (95%CI) 12.326 (3.212-47.306)]. **Conclusion:** Metformin was well tolerated and had encouraging results for patients with advanced prostate cancer.

Key words: Metformin, prostate cancer, androgen deprivation therapy, antineoplastic activities, tumor progression, oral drug

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Prostate cancer represents one of the most common cancers in men and second cause of cancer-related mortality worldwide[1]. Development of prostate cancer usually follows premalignant conditions after transition of normal cells of the prostate into Prostatic Intraepithelial Neoplasia (PIN)[2]. Treatment of prostate cancer always depend on tumor stage, Gleason score and prostatic specific antigen (PSA) level. The 5 year survival rates for cases diagnosed with early localized disease reach approximately[3] about 100%. Unfortunately, most cases came with advanced stage disease in which the aim of treatment is palliation and prevention of disease progression. Androgen Deprivation Therapy (ADT) is the main stay in treatment of advanced stage prostate cancer but most patients showed disease progression 12-18 months after treatment which termed Castration Resistant Prostate Cancer (CRPC)[4]. So, the main aim for management of such cases is to delay disease progression through delaying in development of new metastasis, biochemical failure and castrate-resistant prostatic carcinoma[5]. As known, metformin is a familiar oral drug, cheap and available in all places for patients and health care providers, mainly used for treatment of type 2 diabetes mellitus (T2DM), appeared in pre-clinical researches to have anti-neoplastic effects in prostate cancer[5-8]. Also, it is noted that there is reduction in development of prostate cancer in patients with T2DM receiving metformin, although the epidemiological studies showed that development of prostate cancer is inversely associated with T2DM[9,10]. The mechanisms by which metformin exhibit its effect to reduce prostatic cancer development and progression was supposed and evidenced in many preclinical and clinical studies, preclinical studies showed that metformin inhibit the progression of prostatic carcinoma via modification of both oncogenes and tumor suppressor gene[11], also, it is observed that metformin activate enzyme protease that involved in cancer development through insulin and non-insulin-dependent mechanisms[12,13], it is believed to play a role in androgen receptors down-regulation with subsequent enhancement of the effect of ADT[14]. Regarding hyperinsulinemia and insulin resistance resulted from ADT; it is believed that both lead to increase in free androgens and development of castration resistant prostatic carcinoma[15]. As Egypt is a developing country and most of new expensive targeted therapy not feasible and based on these findings, along with pre-clinical and clinical studies that support the use of metformin for patients with advanced prostate cancer, this study was conducted to evaluate the effect of familiar and cheap drug in Egyptian patients with advanced prostate cancer.

MATERIALS AND METHODS

Eligibility: Patients with histologically and radiologically proved advanced prostate cancer either treatment naive or progressed on previous standard of care (SOC) treatment, other inclusion criteria; adequate organ functions, ECOG performance status (PS) 0-2, no previous metformin therapy in patients progressed on SOC, patient was excluded if had other malignancies in the body elsewhere, known or developed hypersensitivity to metformin, age less than 18 years. The protocol of this study was approved by local ethical committee in institution and signed informed consent from every participant was taken.

Study design and treatment protocol: This is a phase II single-arm clinical study evaluating the effect of metformin therapy in patients with advanced prostate cancer. Metformin was administered as glucophage 1000 mg/twice daily concomitantly with SOC treatment continuously till disease progression, drug toxicity, patient refusal. The SOC treatment involved androgen deprivation therapy (ADT), palliative radiotherapy, bone targeted agents (zoledronic acid or denosumab) and other supportive measures if needed.

Treatment evaluation and patients follow up: Patients were monitored monthly for compliance of treatment, any deterioration in performance status, PSA level and drug related-side effects according to National Cancer Institute Common Terminology Criteria for Adverse[16] Events v.4.03. Disease progression was evaluated every 3 months by physical examination, imaging studies (CT or MRI of chest and pelvic-abdomen, isotopic bone scan), biochemical analysis (CBC, LFTs, KFTs, ALP) according to recommendations of Prostate Cancer Clinical Trials Working[17] Group 2. Other special investigations included PSA doubling time, testosterone level and Body Mass Index (BMI).

End points: The primary end point of the study was time-to-tumor progression (TTP), where the secondary end points were effect of addition of metformin to SOC on development of Castration Resistant Prostate Cancer (CRPC), Overall Survival (OS) and safety of the drug.

Statistical analysis: All statistics were performed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA) and MedCalc windows (MedCalc Software bvba 13, Ostend, Belgium). Time to tumor progression (TTP) was calculated from date of baseline evaluation to date of disease progression. Overall Survival (OS) was calculated as the time from diagnosis to

death or the most recent follow-up contact (censored). Stratification of OS and TTP were done according to all histories of previous SOC. These time-to-death distributions were estimated using the method of Kaplan-Meier plot and compared using two-sided exact log-rank test. All tests were two sided. P-value <0.05 was considered significant.

RESULTS

Patients characteristics: The clinico demographic parameters of patients included in this study were shown in Table 1. The median age of the patients was 65 years, range 59-75, the median Body Mass Index (BMI) was 24.75 ranges 17-40, 18 cases of this study had ECOG PS of one and the remaining cases were ECOG 2. Regarding the site of metastasis, most cases had bone metastasis (80.8%), although other sites were involved with relative frequencies. Before starting the treatment, the median PSA level was 184.40 range (27-700). In this study, there were 17 treatment naïve cases and 9 cases were subjected to previous SOC treatment.

Treatment outcome: After median follow-up of 9.5 months range (4-36), there were 14 patients of 26 still alive. Regarding the treatment response, the overall response (CR, PR) was 53.8%; No response (SD, PD) represented 46.2%, also, this study showed that 50% of cases progressed after 18 weeks of starting the treatment. It was also noted that the media PSA post treatment was 30 ranges (1-100) with percent median change of -70%, the median time to tumor progression (TTP) was 18 weeks but it was significantly differed in previously treated cases and treatment naive cases, in which median TTP in previously treated case was 8 weeks compared to 32 weeks in treatment naïve cases [p<0.001, HR (95%CI) 12.326 (3.212-47.306)] (Table 1).

Univariante analysis was performed to detect the effect of patient's variables on response of treatment and disease progression, it is noted that, there is no significant impact of age, BMI, PS, site metastasis and pre-treatment PSA level on treatment response, also, the effect of these variables on TTP was analyzed and there is insignificant effect was noted. Relation between previous SOC treatment and treatment outcome was analyzed also, it is noted that, cases who are

Table 1: Baseline characteristics and outcome of the studied patients

	All patients (N = 26)			All patients (N = 26)	
Parameters	No.	%	Parameters	No.	%
Age			**Liver metastasis**		
Mean±SD	65.57±4.25		Absent	23	88.5
Median (range)	65(59-75)		Present	3	11.5
≤65 years	14	53.8	**SOC previous**		
>65 years	12	46.2	Absent	17	65.4
BMI			Present	9	34.6
Mean±SD	25.64±6.62		**PSA post-treatment**		
Median (range)	24.75(17-40)		Mean±SD	32.73±28.34	
Underweight	3	11.5	Median (range)	30(1-100)	
Average	10	38.5	≤30 ng mL^{-1}	15	57.7
Overweight	8	30.8	>30 ng mL^{-1}	11	42.3
Obese	5	19.2	**PSA change ()**		
ECOG PS			Mean±SD	-51.48±49.66	
ECOG 1	18	69.2	Median (range)	-70(-98-78.57)	
ECOG 2	8	30.8	**Response**		
PSA pre-treatment			CR	2	7.7
Mean±SD	140.76±64.50		PR	12	46.2
Median (range)	184.40(27-700)		SD	7	26.9
≤60 ng mL^{-1}	12	46.2	PD	5	19.2
>60 ng mL^{-1}	14	53.8	OAR	14	53.8
Bone metastasis			NR	12	46.2
Absent	5	19.2	**Follow-up (months)**		
Present	21	80.8	Mean±SD	16.19±11.13	
LN metastasis			Median (range)	9.50(4-36)	
Absent	21	80.8	**Progression**		
Present	5	19.2	Before 18 weeks	13	50
Lung metastasis			After 18 weeks	13	50
Absent	20	76.9	**Mortality**		
Present	6	23.1	Alive	14	53.8
			Died	12	46.2

Continuous variables were expressed as Mean±SD and median (range), Categorical variables were expressed as number (percentage)

Table 2: Univariate predictors of response

			Response								
	All patients (N = 26)		CR (N = 2)		PR (N = 12)		SD (N = 7)		PD (N = 5)		
Parameters	No.	%	No.	%	No.	%	No.	%	No.	%	p-value
Age											
≤65 years	14	53.8	2	14.2	5	35.7	5	35.7	2	14.3	0.297‡
>65 years	12	46.2	0	0	7	58.3	2	16.7	3	25.0	
BMI											
Underweight	3	11.5	0	0	2	66.7	0	0	1	33.3	0.752§
Average	10	38.5	1	10.0	5	50.0	3	30.0	1	10.0	
Overweight	8	30.8	1	12.5	3	37.5	1	12.5	3	37.5	
Obese	5	19.2	0	0	2	40.0	3	60.0	0	0	
ECOG PS											
ECOG 1	18	69.2	1	5.6	8	44.4	5	27.8	4	22.2	0.880‡
ECOG 2	8	30.8	1	12.5	4	50.0	2	25.0	1	12.5	
PSA pre-treatment											
≤60 ng mL^{-1}	12	46.2	1	8.3	3	25.0	3	25.0	5	41.7	0.045‡
>60 ng mL^{-1}	14	53.8	1	7.1	9	64.3	4	28.6	0	0	
Bone metastasis											
Absent	5	19.2	1	20.0	3	60.0	1	20.0	0	0	0.427‡
Present	21	80.8	1	4.8	9	42.9	6	28.6	5	23.8	
LN metastasis											
Absent	21	80.8	2	9.5	9	42.9	5	23.8	5	23.8	0.509‡
Present	5	19.2	0	0	3	60.0	2	40.0	0	0	
Lung metastasis											
Absent	20	76.9	0	0	9	45.0	6	30.0	5	25	0.037‡
Present	6	23.1	2	33.3	3	50.0	1	16.7	0	0	
Liver metastasis											
Absent	23	88.5	2	8.7	9	39.1	7	30.4	5	21.7	0.266‡
Present	3	11.5	0	0	3	100	0	0	0	0	
Previous SOC											
Absent	17	65.4	2	11.8	10	58.8	4	23.5	1	5.9	0.057‡
Present	9	34.6	0	0	2	22.2	3	33.3	4	44.4	
PSA post-treatment											
≤30 ng mL^{-1}	15	57.7	2	13.3	7	46.7	5	33.3	1	6.7	0.178‡
>30 ng mL^{-1}	11	42.3	0	0	5	45.5	2	18.2	4	36.4	

Categorical variables were expressed as number (percentage), CR: Complete response, PR: Partial response, PD: Progressive disease, SD: Stable disease, SOC: Standard of care, ECOG: Eastern cooperative oncology group, PSA: Prostatic specific antigen, ‡Chi-square test, §Chi-square test for trend, p<0.05 is significant

treatment naïve had longer TTP and OS than those subjected to previous SOC treatment (p<0.001) (Table 2). Metformin was tolerated and treatment-related side effects were minimal and easily manageable where grade 3 or 4 adverse effects not occurred during the period of treatment.

DISCUSSION

Androgen deprivation therapy (ADT) is the main stay and universally accepted first line of treatment in advanced prostate cancer[18]. The main problem for such patients was that, after the initial response to treatment, most cases showed treatment failure either clinically or biochemically and so the results of current lines of treatment for advanced prostate cancer are limited either due to drug resistance or toxicities that may develop by the time, thus, novel molecular targets and new therapeutic agents are needed[19]. The role of metformin in management of prostate cancer was investigated in many retrospective and prospective studies both for metastatic and non-metastatic cases and discussed in systematic reviews[2,5,20-22], the aim of those studies was to evaluate the efficacy of metformin on biochemical failure, disease progression, metastases and evolution to CRPC. This is the 1st research conducted to assess the effect of metrformin on Egyptian patients with advanced prostate cancer. In Egypt as a developing country the problem in such cases is that, when these cases developed CRPC the new approved lines of treatment was not available and expensive to be feasible for these patients, so, the aim is to find an agent that could be available and easy accessible, hence, this study was conducted to evaluate metformin, a very familiar drug for both patients and physicians to find its benefits for patients.

The limitations of this clinical study is the lack of a control group for comparison of the effect of metformin on treatment group, also, the study involved both treatment naïve and previously treated cases with advanced prostate cancer which may resulted in some bias in certain correlations. The results showed that, use of metformin in present cases resulted in improvement of time to tumor progression (TTP), specially in treatment naïve patients, these results also were established in Rothermundt *et al.*[23] study in which metformin was evaluated for its efficacy in patients with CRPC and they concluded that metformin was safe and had objective responses and its activity encouraged further studies as a therapy for prostate cancer management. Also, in current results in treatment naïve patients, metformin had significant objective response in both TTP and biochemical failure which also achieved in Spratt *et al.*[24] study in which they investigated the efficacy of metformin to reduce the development of CRPC and related mortality. The previous two big studies are the 1st studies that evaluate the role of metformin in prostate cancer, although, these studies had certain limitations, they are considered to be the nucleus for next studies and the original references for it. In this study, the effect of patients and tumor characteristics on the response of treatment was evaluated, however it expected that certain variables as age, BMI, PS, pre-treatment PSA and site of metastasis will affect the treatment response, statistical analysis showed insignificant effects of all except pre treatment PSA which had statistically significant effect ($p = 0.045$) but post-treatment PSA had insignificant effect ($p = 0.178$) this results differed from that obtained by Seo *et al.*[25] retrospective multicentre Korean study that indicate post PSA nadir of ≤ 0.2 ng mL^{-1} showed better progression-free survival, this difference may be due to evaluation of different patients groups as it involved both advanced and locally advanced cases. Although many prospective studies evaluating the effect of metformin in prostate cancer are growing, the final reports on survival outcome not yet developed and hence the results of this study will be added and help in detecting the role of this familiar and hopeful drug in management of prostate cancer, despite some limitations mentioned before that could be corrected in the future studies.

CONCLUSION AND RECOMMENDATION

Metformin was appeared to be marginally beneficial in decreasing risks of biochemical failure in patients with advanced prostate cancer. Although there are certain limitations in this study, the results are encouraging and were supported by other previous studies, however additional randomized control studies are needed to assess the exact efficacy of metformin for patients with advanced prostate cancer.

SIGNIFICANCE STATEMENT

This study discovered that metformin could be beneficial for patients with advanced prostate cancer and will help the researchers to uncover the critical areas in that era of research that many researchers were not able to explore. Thus a new theory on anti-neoplastic activity of metformin especially in prostate cancer may be arrived at.

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