A Retrospective Study of the Effect of Metformin on Patients with Metastatic Prostate Cancer

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ABSTRACT

INTRODUCTION: Previous studies demonstrated that metformin could lead to an inhibition of proliferation of cancer cells through a shift from anabolic to catabolic metabolism. In this study, we seek to investigate the effect of metformin in metastatic prostate cancer.

METHODS: Patients followed at Northwell Health Zuckerberg Cancer Center during 2014-2018 were included if they were diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC) or metastatic castration-resistant prostate cancer (mCRPC), with ⩾6 months follow-up with and without metformin treatment. The primary outcomes, 6-month prostate-specific antigen (PSA) response, overall survival (OS), and radiographic progression free survival (rPFS), were evaluated.

RESULTS: There were 267 patients included in the final analysis; 196 patients had mHSPC (73.2%) and 71 had mCRPC (26.8%). Within the mHSPC subjects, there was a significant difference in OS between metformin vs nonmetformin groups (148.5 vs 85.6 months; $P < .046$) in a univariate analysis; patients who took metformin had a significantly longer OS than subjects who did not (median OS: 148.5 vs 86 months; $P < .046$). There was no significant difference between the 2 groups with respect to either PSA response rate at 6 months or rPFS or OS in patients with mHSPC in both univariate and multivariate analysis. Within the mCRPC subjects, there was no significant difference between metformin and nonmetformin groups with respect to OS (43.3 vs 51.5 months; $P < 0.160$) or PSA response at 6 months (38.5% vs 57.1%; $p < 0.24$); however, patients on metformin had a significantly shorter rPFS in both the univariate analysis (7.3 vs 17.4; $P < .0002$) and in the multivariate analysis (HR = 2.52; 95% CI: 1.24m 5.11; $P < .0109$).

CONCLUSIONS: Among patients with mHSPC, use of metformin was not significantly associated with improved OS in the multivariate analysis.

KEYWORDS: Metformin, metastatic hormone-sensitive prostate cancer, metastatic castration-resistant prostate cancer

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Introduction

Prostate cancer is the second most common cancer with 34 130 estimated deaths and 248 530 estimated new cases in 2021.[1] Localized prostate cancer can be cured with surgery or radiotherapy, but many patients relapse with distant metastasis. The remainder of patients, however, are considered to have incurable advanced disease.[2]

Currently, the standard of care for mHSPC is androgen deprivation therapy (ADT) alone or plus docetaxel or abiraterone/prednisone or enzalutamide or apalutamide. In mCRPC, the standard of care is ADT plus abiraterone/prednisone, or enzalutamide, or olaparib, or sipuleucel T, or radium 223, or docetaxel or cabazitaxel or lutetium-177-PSMA. However, most of these treatments mainly target androgen pathway or chemotherapy or radiotherapy with short survival benefits. We need to develop a new targeted therapy.

Several studies have reported the potential antineoplastic activity of metformin, a quite common and benign antihyperglycemic agent, in reducing the incidence of colon, breast, pancreatic, and prostate cancer.[3-7] However, its effect on patients with advanced prostate cancer remains unclear. Metformin use was associated with a lower risk of death due to the cancer.[8-12] However, 1 study showed negative result, though this discrepancy may be due to each study's characteristic of patient populations.[13] There is a prospective, randomized, phase III STAMPEDE trial ongoing in patients with locally advanced and metastatic hormone-naïve prostate cancer with ADT plus metformin as compared with ADT alone. Metformin can activate AMP-activated protein kinase (AMPK), which can decrease insulin secretion, inhibit gluconeogenesis and energy consuming processes, and stimulate ATP-generating processes.[14] Metformin binds PEN2 to initiate the signaling

pathway that crosstalks with the lysosomal glucose-sensing pathway for AMPK activation through ATP6AP1.[15] These effects lead to an inhibition of proliferation of cancer cells through a shift from anabolic to catabolic metabolism.[16] In this study, we seek to investigate the effect of metformin in metastatic prostate cancer.

Material and methods

Trial design and patients

This was an institutional review board-approved retrospective chart review conducted at Northwell Health Zuckerberg Cancer Center. Patients were included in the study if they had metastatic prostate cancer and were seen by our practice with ⩾6 months follow-up between January 2014 to December 2018. Patients were excluded from analysis if they had active or history of another cancer, or if insufficient information was available in the electronic medical records. Patients were then stratified into either mHSPC or mCRPC. Within both of these groups, patients were further classified to those who received metformin at any point versus those who did not.

Electronic medical records were accessed to collect data patient demographics, including age, ethnicity, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status (PS), treatment history, and presence of bone or visceral metastasis at the time of metastatic prostate cancer diagnosis. rPFS was evaluated based on the Prostate Cancer Working Group 3 (PCWG3) and Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[17,18] Prostate-specific antigen (PSA) response rate at 6 months was defined as ⩾50% decrease from baseline after initiation of treatment. The definition of rPFS is based on PCWG3 and modified RECIST progression criteria of soft tissue lesions measured by CT or MRI and death from any cause. Furthermore, overall survival (OS) was also evaluated in this study.

Study data were collected and managed using Research Electronic Data Capture (REDCap). REDCap is a secure, web-based application designed to support data capture for research studies, providing an intuitive interface for validated data entry, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages, and procedures for importing data from external sources.[19]

Statistical analysis

All analyses were conducted separately according to metastatic disease group, namely, the Hormone-Sensitive [mHSPC] and the Castrate-Resistant [mCRPC] prostate cancer subjects. These disease groups are inherently clinically distinct types of metastatic cancer and therefore, it was deemed appropriate to conduct all analyses in parallel. Outcomes of interest (survival, rPFS, and PSA response rates) were compared between metformin and nonmetformin groups according to disease type. Time-to-event was calculated as the number of months from the start of treatment to the event of interest (eg, death or progression). Subjects who did not reach the event of interest were considered censored and the number of months until the last follow-up was used.

Median follow-up time was calculated using the method of Schemper and Smith.[20] Fisher's exact test was used to compare the PSA response rates between metformin groups. A multivariate logistic regression was used to examine differences in PSA response rates between metformin groups, adjusting for age, ECOG performance score, and presence of visceral metastasis. The Kaplan-Meier Product Limit Method and the Cox proportional hazards regression were used to analyze overall survival and rPFS. Log rank test was used to compare the overall survival and rPFS between Metformin groups. A multivariate Cox regression analysis for both OS and rPFS, with age, ECOG performance score and presence of visceral metastasis, was carried out. Interaction effects were examined. All analyses were generated using SAS v9.4 (SAS Institute, Cary, NC).

Results

A total of 583 patients were identified and 316 patients were excluded (201 patients due to presence of another cancer, 95 patients due to insufficient information from the electronic medical records, and 20 patients had <6 months of follow-up), leaving 267 patients included for the final analysis (Figure 1). The median age at prostate cancer metastasis was 73 (range, 46-100) years with approximately half of the patients white (50.7%) and the majority had an ECOG PS of 0/1 (73.2%). Further baseline demographics are described in Table 1. One hundred and ninety-six patients had mHSPC (73.2%) and 71 had mCRPC (26.8%). Sixty-four patients were taking metformin (24%) and 203 were not (76%). The median daily dose of patients taking metformin was 1000 mg [range, 500-2000 mg]. Eleven percent of patients were taking 500 mg daily, 2% 850 mg daily, 58% 1000 mg daily, and 2% 1700 mg daily, and 28% 2000 mg daily. All patients in the metformin group were taking metformin throughout their history of prostate cancer.

The median follow-up time was 44.3 months for the mHSPC group [95% confidence interval (CI) 37.1-49.9]; and 32.0 months for mCRPC [95% CI: 26.7-46.6] Within the mHSPC group, the 6 month PSA response rates with and without metformin use were 80.5% and 79.3%, respectively ($P < .867$). Within the mCRPC group, the 6 month PSA response rates with and without metformin use were 38.5% and 57.1%, respectively ($P < .238$).

In the unadjusted analysis, OS was significantly longer in the metformin users than in the nonmetformin users within the mHSPC group (median survival: 148.5 (95% CI: 120.4 to n.e.) vs 85.6 (95% CI: 57.5 to n.e.; $P < 0.046$) (Figure 2A) but not within the mCRPC group (median survival: 43.4 (95% CI: 25.3 to n.e.) vs 51.5 (95% CI: 39.7-69.4); $P < .160$) (Figure 2B). Due to the pattern of the data, the upper limits of some of

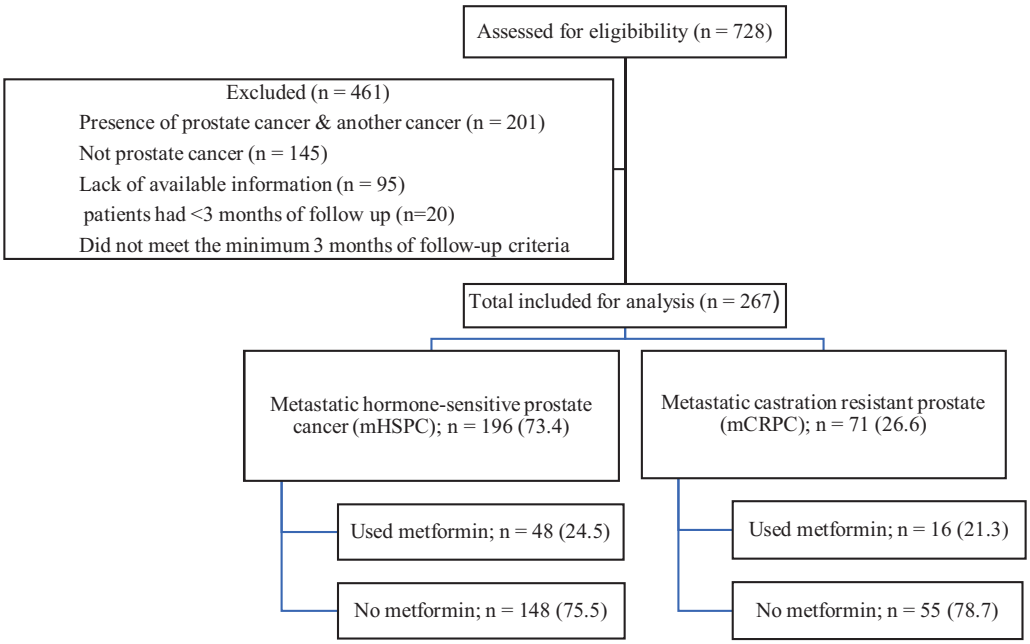

Figure 1. Patient stratification.

the confidence intervals were not estimable (n.e.). The multivariate Cox regression analysis adjusting for age, ECOG, and visceral metastasis, showed that OS was no longer significantly different between the 2 groups within the mHSPC group ($P < .2320$) and remained not significantly different in the mCRPC group ($P < 0.4930$).

In the unadjusted analysis, rPFS did not differ between metformin and nonmetformin users within the mHSPC group (19.6 (95% CI: 14.0-30.0) vs 17.9 (95% CI: 14.3-24.5)months; $P < .682$) (Figure 3A); rPFS was significantly shorter in the metformin users than in the nonmetformin users within the mCRPC group (median time-to-progression: 7.3 (95% CI: 6.0-11.5)) vs 17.4 (95% CI: 13.1-24.1); $P < .0002$) (Figure 3B). The multivariate Cox regression analysis showed that rPFS was not significantly different between the 2 groups ($P < 0.8273$ in the mHSPC group. The multivariate analysis of OS in HSPC group is summarized in Table 2. Within the mCRPC group, the multivariate Cox regression analysis showed that rPFS remained significantly different between the 2 groups ($P < .0109$) (HR = 2.52; 95% CI: 1.24-5.11).

Discussion

Our data suggest that metformin treatment was significantly associated with improved OS, but not with PSA response rate or rPFS within mHSPC in a univariate analysis. A suggestive difference between metformin and nonmetformin groups with respect to OS was observed only within mHSPC, but not within mCRPC group. on a multivariate analysis the same OS benefit was not seen between the 2 groups. In patients with mHSPC, the distributions of performance status, age and visceral metastasis were comparable between metformin groups (Table 1), but we included them in the multivariate analysis to examine their joint effect in the model. The interaction effect of metformin and performance score as well as metformin and visceral metastasis were examined, and neither were statistically significant (which may be due to some power issue), hence only the main effects were included in the model. Results showed that there was a significant effect of both performance status ($P < .0009$) and visceral metastasis ($P < .0004$) on OS. Higher (worse) performance status and the presence of visceral metastasis were each associated with worse OS (HR = 3.33; 95% CI: 1.64-6.78 and HR = 2.87; 95% CI: 1.59-5.165, respectively). The result suggests that the subgroup of patients without visceral metastasis may get the benefit, warranting further prospective studies such as a multiarm, multistage, and randomized phase III controlled STAMPEDE trial group K for men with high-risk locally advanced or mHSPC.[21] Metformin potentially targets Insulin like Growth Factor (IGF) and PI3 K-AKT pathway which plays an important role in initiating the progression of advanced prostate cancer.[22] One phase 2 study indicated that metformin may play a role in disease stabilization and prolongation of PSA doubling time in some patients with mCRPC.[23] There are around 30 clinical trials associated with metformin effect on neoadjuvant, adjuvant setting for localized prostate cancer, biochemical recurrence, mHSPC, and mCRPC. This may open a new avenue to target metabolic pathway for treating metastatic hormone-sensitive prostate cancer besides androgen receptor pathway.

Furthermore, cells with PTEN loss in mouse model increased dramatic sensitivity to metformin killing to cells.[24] Given PTEN loss rate almost in half patient populations in advanced prostate cancer, it may provide strong evidence why metformin efficacy is so high to prolong patient survival. We have an institutional approved protocol that PTEN loss as a

Table 1. Baseline demographics and characteristics.

CHARACTERISTIC, MEDIAN (RANGE)	MHSPC (N = 196)		MCRPC (N = 71)	
	METFORMIN (N = 48)	NO METFORMIN (N = 148)	METFORMIN (N = 16)	NO METFORMIN (N = 55)
Age, years	70 (50-90)	72.5 (46-100)	78 (56-86)	76 (58-100)
BMI	30.5 (15.7-47)	27.3 (17.8-3.3)	29.1 (19.1-39.7)	27 (18.4-40.2)
Race, n (%)				
White	21 (43.8)	77 (52.0)	9 (56.3)	27 (49.1)
Black	10 (20.8)	27 (18.2)	4 (25)	13 (23.6)
Asian	2 (4.2)	10 (6.8)	0 (0)	1 (1.8)
More than 1 race	1 (2.1)	0 (0)	0 (0)	0 (0)
Unknown	14 (29.2)	34 (23.0)	3 (18.8)	14 (25.5)
ECOG performance status, n (%)				
0	20 (44.4)	68 (46.9)	6 (42.9)	15 (27.8)
1	16 (35.6)	39 (26.9)	3 (21.4)	21 (38.9)
2	5 (11.1)	25 (17.2)	2 (14.3)	7 (13.0)
3	4 (8.9)	9 (6.2)	3 (21.4)	10 (18.5)
4	0 (0)	4 (2.8)	0 (0)	1 (1.9)
Number of previous hormonal treatments, n (%)				
0	1 (2.1)	3 (2.0)	0 (0)	0 (0)
1	11 (22.9)	34 (23.0)	0 (0)	2 (3.6)
2	16 (33.3)	48 (32.4)	5 (31.3)	5 (9.1)
>2	20 (41.7)	63 (42.6)	11 (68.8)	48 (87.3)
Number of previous chemotherapy, n (%)				
0	30 (62.5)	97 (65.5)	9 (56.3)	33 (60.0)
1	12 (25.0)	34 (23.0)	5 (31.3)	11 (20.0)
2	4 (8.3)	11 (7.4)	2 (12.5)	8 (14.5)
>2	2 (4.2)	6 (4.1)	0 (0)	3 (5.5)
Receive docetaxel at any point	17 (35.4)	47 (31.8)	5 (31.3)	20 (36.4)
Bone metastases	38 (79.1)	124 (83.8)	15 (93.8)	47 (85.5)
Visceral metastases	5 (10.4)	32 (21.6)	6 (37.5)	8 (14.5)
Treated with radical prostatectomy	21 (43.8)	44 (29.7)	3 (18.8)	12 (21.8)
Gleason score, n (%)				
3 + 3	4 (9.8)	8 (7.1)	2 (15.4)	7 (15.6)
3 + 4	1 (2.4)	12 (10.6)	0 (0)	8 (17.8)
3 + 5	0 (0)	1 (0.9)	1 (7.7)	0 (0)
4 + 3	10 (24.4)	22 (19.5)	2 (15.4)	6 (13.3)
4 + 4	10 (24.4)	19 (16.8)	3 (23.1)	11 (24.4)
4 + 5	7 (17.1)	23 (20.4)	3 (23.1)	8 (17.8)
5 + 3	0 (0)	1 (0.9)	0 (0)	0 (0)
5 + 4	8 (19.5)	18 (15.9)	1 (7.7)	5 (11.1)
5 + 5	1 (2.4)	9 (8.0)	1 (7.7)	0 (0)

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer.

biomarker to predict a response to metformin therapy in patients with advanced prostate cancer. By doing this study, we may elucidate which patients will get the benefit from metformin management. PTEN loss may not be a unique mechanism given the fact that PTEN loss occurs both in mHSPC and mCRPC.

There are several limitations to our study. This was a retrospective study based on available data and was not based on any

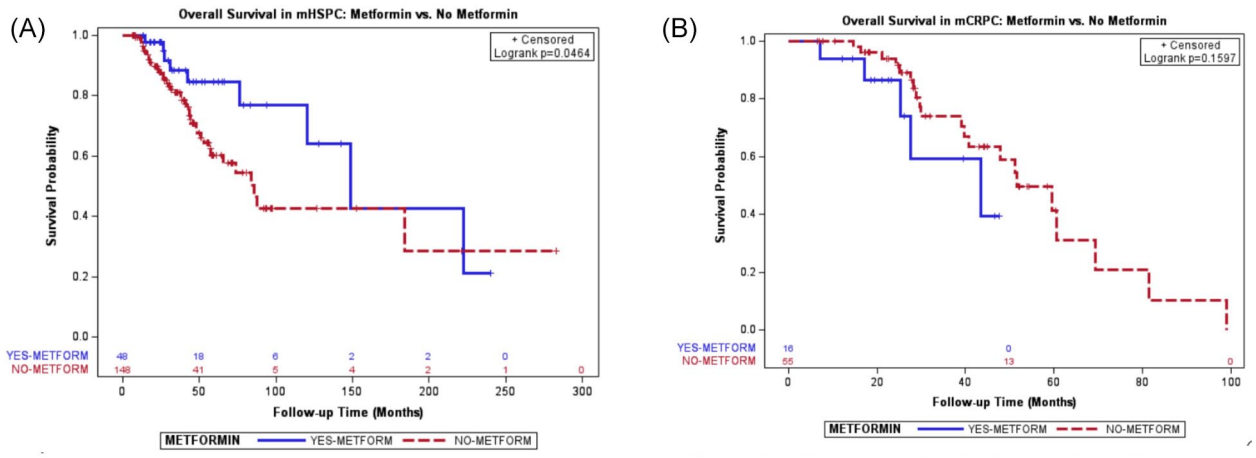

Figure 2. (A) Kaplan-Meier estimate of median overall survival in mHSPC. (B) Kaplan-Meier estimate of median overall survival in mCRPC
mCRPC indicates metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer.

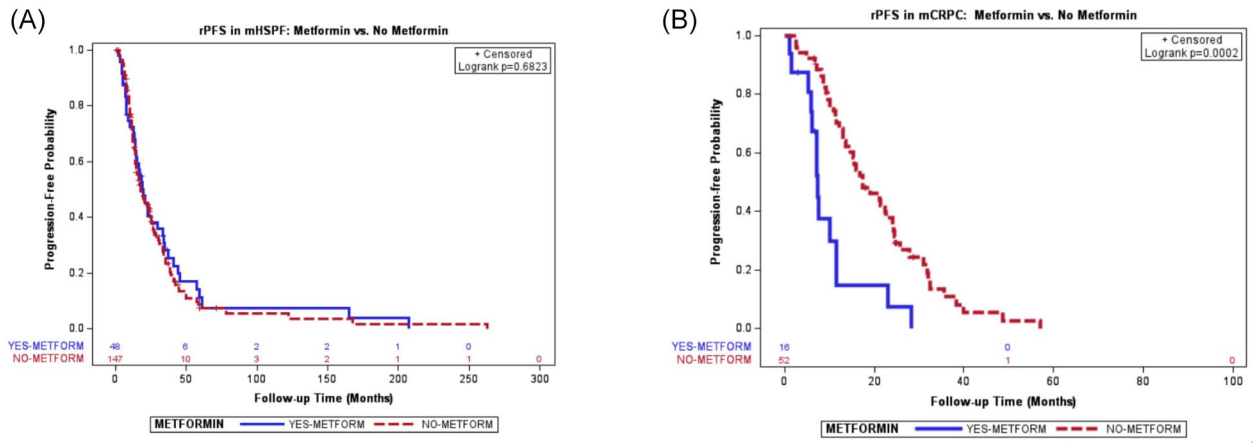

Figure 3. (A) Kaplan-Meier estimate of median progression free survival in mHSPC. (B) Kaplan-Meier estimate of median progression free survival in mCRPC.
mCRPC indicates metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer.

Table 2. Multivariate analysis of overall survival in hormone-sensitive prostate cancer patients.

VARIABLE	HAZARD RATIO	95% CI	*P*-VALUE
Metformin (ref: no metformin)	0.635	0.301-1.337	0.232
Age	1.013	0.985-1.042	0.352
ECOG PS Group (ref: ECOG=0, 1, 2)	3.335	1.640-6.784	0.0009
Visceral metastasis (ref: none)	2.873	1.598-5.165	0.0004

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

formal power calculations. The dose and duration of metformin treatment was unknown, and metformin-treated patients almost all had diabetes.

Conclusions

Metformin is a safe and effective antidiabetic agent with many potential uses currently being studied across several different disease states. The OS benefit in mHSPC patients taking metformin observed in a univariate analysis but not a multivariate analysis suggests that the addition of metformin to prostate cancer therapy may be useful. Further studies are needed to0020examine whether use of metformin may be more beneficial in the management of patients without visceral metastasis. Although rPFS and 6-month PSA response had negative results, this study may warrant prospective randomized trials involving metformin, and more specific studies involving PTEN loss in the future.

Author Contributions

Study design and conception: Chung-Shien Lee and Xin-Hua Zhu
Data acquisition: Chung-Shien Lee, So Yi Lam, Wingsze Liu, Xin-Hua Zhu

Data analysis: Chung-Shien Lee, So Yi Lam, Wingsze Liu, Cristina Sison, Xin-Hua Zhu

Interpretation and critical review of the data: Chung-Shien Lee, So Yi Lam, Wingsze Liu, Cristina Sison, Xin-Hua Zhu

Drafting or revision of the manuscript for important intellectual content: Chung-Shien Lee, So Yi Lam, Wingsze Liu, Cristina Sison, Xin-Hua Zhu

Approved the version to be published: Chung-Shien Lee, So Yi Lam, Wingsze Liu, Cristina Sison, Xin-Hua Zhu

Ethical Approval

This study was approved by Northwell Health Cancer Institute Ethical Committee on February 11, 2019, ID# 19-0097.

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