Impact of Addition of Metformin to Abiraterone in Metastatic Castration-Resistant Prostate Cancer Patients With Disease Progressing While Receiving Abiraterone Treatment (MetAb-Pro): Phase 2 Pilot Study

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Abstract

Treatment patterns for advanced prostate cancer have changed in recent years. This additional analysis in 25 men provides evidence of no clinical benefit of the addition of metformin to abiraterone for patients with metastatic castration-resistant prostate cancer who experience prostate-specific antigen progression while receiving therapy with abiraterone.

Background: There is evidence linking metformin to improved prostate cancer–related outcomes. **Patients and Methods:** Twenty-five men with metastatic castration-resistant prostate cancer and prostate-specific antigen (PSA) progression while receiving treatment with abiraterone from 3 Swiss centers were included in this single-arm phase 2 trial between November 2013 and September 2016. Metformin was added to abiraterone continuously at 1000 mg twice daily in uninterrupted 4-week cycles. The primary end point was the absence of disease progression at 12 weeks (PFS12). The Fleming single-stage design was applied. With a 5% significance level and 80% power, 25 patients were required to test PFS12 $\leq$ 15% (H0) compared to $\geq$ 35% (H1). Secondary end points included toxicity and safety issues. The study was registered at ClinicalTrials.gov (NCT01677897). **Results:** The primary end point PFS12 was 12% (3 of 25 patients) (95% confidence interval, 3-31). Most patients had PSA progression, almost half had radiographic progression, but only 1 patient had symptomatic progression. Eleven (44%) of 25 patients had grade 1 and 2 patients each grade 2 (8%) or grade 3 (8%) gastrointestinal toxicity (nausea, diarrhea, loss of appetite). One patient discontinued treatment at week 5 because of intolerable grade 3 diarrhea. **Conclusion:** The addition of metformin to abiraterone for patients with metastatic castration-resistant prostate cancer and PSA progression while receiving abiraterone therapy does not affect further progression and has no meaningful clinical benefit. A higher-than-expected gastrointestinal toxicity attributed to metformin was observed.

Keywords: Abiraterone acetate, Metastatic prostate cancer, Metformin, mTOR inhibition, PSA progression

Introduction

Metastatic prostate cancer is highly castration sensitive, and therefore androgen-deprivation therapy (ADT) is the treatment of choice. Yet virtually all patients experience disease progression while receiving ADT and develop metastatic castration-resistant prostate cancer (mCRPC). For many years, chemotherapy with docetaxel

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represented the standard of care in first-line treatment of mCRPC, but androgen signal inhibitors (ASI) such as abiraterone acetate and enzalutamide have recently been introduced as standard first-line treatments in mCRPC.[1]

Abiraterone acetate, a prodrug of abiraterone, is a selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450c17 (CYP17), a critical enzyme in testosterone synthesis. CYP17 inhibition effectively suppresses the androgen synthesis in the adrenal glands and the testes, and most importantly within the prostate cancer tissue.[2,3] Daily oral administration of 1000 mg abiraterone plus 10 mg of prednisone showed a significantly improved survival in patients with mCRPC who were treatment naive compared to prednisone alone.[4] On the basis of these results, abiraterone has become one of the preferred first-line treatments for men with asymptomatic or mildly symptomatic mCRPC.

Patients receiving first-line abiraterone can have primary resistance to the treatment, but most patients develop acquired resistance, and a prostate-specific antigen (PSA) rise is noted after a median of 11 months after initiating treatment. Androgen receptor (AR)-dependent (eg, splice variants, AR overexpression, AR mutations) and AR-independent mechanisms can lead to resistance against novel ASI drugs such as abiraterone or enzalutamide.[5,6] AR-independent resistance can occur through cross-talk signaling via the PI3K/AKT/mTOR growth factor receptor pathway.[7] A cell line experiment suggested that blockade of both AR and mammalian target of rapamycin (mTOR) pathways might restore sensitivity to antiandrogen treatment.[8] This observation was supported by the results of a xenograft model[9]: the addition of the mTOR inhibitor everolimus to the antiandrogen bicalutamide restored the sensitivity of androgen-resistant tumors and led to reduced growth rates and tumor volumes.

Metformin (1.1-dimethylbiguanide hydrochloride) belongs to the biguanide class of oral hypoglycemic agents and is an often-prescribed medication for type 2 diabetes. It lowers glucose production through inhibition of gluconeogenesis and by reducing the rate of hepatic glycogenolysis.[10] Retrospective cohort studies have revealed a reduced risk of prostate cancer development, recurrence, and prostate cancer–related mortality. Several in vitro and in vivo studies have demonstrated that metformin can result in anticancer activity in different types of cancer, including prostate cancer.[11,12] The main mechanism of action through which metformin inhibits tumor growth appears to be activation of AMP-activated protein kinase (AMPK).[13,14] AMPK is a key regulator of the cellular response to energy stress.[15,16] AMPK activation leads to downstream inhibition of mTOR signaling.[17] The mTOR complex is an important mediator of the phosphatidylinositol-3-kinase/AKT (PI3K/AKT) pathway, which is linked to cancer cell growth and proliferation.[18]

Two studies have examined the effect of treatment with metformin and the mTOR inhibitor everolimus, respectively, for patients with slowly progressing mCRPC.[19,20] Both agents demonstrated favorable effects as single-agent treatment with PSA responses and disease stabilization, providing clinical evidence that mTOR inhibition might be beneficial in patients with mCRPC.

On the basis of these data, we hypothesized that the addition of metformin could inhibit the acquired ligand-independent resistance to abiraterone and restore sensitivity to abiraterone leading to prolonged progression free survival.

Patients and Methods

MetAb-Pro is a phase 2 pilot study conducted at 3 Swiss centers. Patients were enrolled between November 2013 and September 2016. Eligibility criteria included adenocarcinoma of the prostate, metastatic or locally advanced disease, progression while receiving ADT, castration-level testosterone $\leq$ 50 ng/dL, and PSA progression during treatment with abiraterone (at least 12 weeks of treatment) defined as follows:

- In case PSA levels had not decreased under treatment: $\geq$ 25% increase over baseline (at registration) AND an increase in the absolute PSA value of $\geq$ 5 ng/mL.
- In case of PSA response $<$ 50% under treatment: $\geq$ 25% increase over the nadir AND an increase in the absolute PSA value of $\geq$ 5 ng/mL.
- In case of PSA response $\geq$ 50% under treatment: $\geq$ 50% increase over the nadir AND an increase in the absolute PSA value of $\geq$ 5 ng/mL.

PSA progression had to be confirmed at least 1 week later.

Patients had to be asymptomatic with a World Health Organization performance status of 0 or 1. No evidence of radiologic disease progression, no visceral metastases (mandatory computed tomography/bone scan before study entry), no prior chemotherapy, and no prior use of metformin was allowed.

All patients provided written informed consent. The trial was approved by the local ethics committee, was registered (ClinicalTrials.gov NCT01677897), and followed the current Guidelines for Good Clinical Practice issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use[21] and the Declaration of Helsinki.

Study Design

This single-arm phase 2 trial evaluated the addition of metformin to abiraterone in mCRPC patients who experienced PSA progression while receiving treatment with abiraterone. Abiraterone was administered according to the standard of care: abiraterone acetate 1000 mg every day and prednisone 10 mg every day. Metformin was administered continuously at 1000 mg twice daily in uninterrupted 4-week cycles. The metformin dose was increased stepwise (500 mg steps) within 2 weeks to the target dose. Treatment was continued until progression, unacceptable toxicity, or refusal.

Physical condition, safety, and drug-related toxicities were evaluated on scheduled visits every 4 weeks during trial treatment. Adverse events were defined by National Cancer Institute Common Terminology Criteria for Adverse Events 4.0.[22] Disease status was assessed every 12 weeks with physical examination; computed tomography of the chest, abdomen, and pelvis; bone scan; PSA; and laboratory evaluation in accordance with the Prostate Cancer Clinical Trials Working Group recommendations (PCWG2).[23]

Metabolic parameters were assessed at baseline: body mass index (BMI), glycosylated hemoglobin (HbA1c), fasting glucose, insulin, and C-peptide. A glucose tolerance test was performed before the start of metformin and after 12 weeks.

Statistical Analysis

The study's primary end point was progression-free survival at 12 weeks (PFS12), defined as absence of progression according to the PCWG2 criteria,[23] including PSA increase, progression of measurable disease or bone lesions, clinical progression, start of palliative radiotherapy, or death. Patients without assessment in this time period were counted as having progressive disease unless they had a positive outcome measured at a later date.

The Fleming single-stage design was applied, with chosen thresholds of 15% and 35%. With a 1-sided 5% significance level and 80% power, 25 evaluable patients were required to test PFS12 $\leq$ 15% (H0) compared with $\geq$ 35% (H1). If $\leq$ 8 evaluable patients remained free of progression at 12 weeks by the end of the trial, the trial treatment would be deemed unworthy of further investigation.

Secondary end points were PFS at 24 weeks; progression-free survival (PFS); clinical benefit rate at 12 and 24 weeks, defined as response or stable disease according to the Response Evaluation Criteria in Solid Tumors and clinically stable; PSA response (50% and 30%; and at 12 weeks); overall survival; and toxicity and safety.

Appropriate descriptive measures were used for categorical and numerical variables. Time-to-event end points were analyzed by the Kaplan-Meier method. Analyses were performed by R 3.4 software (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/).

Results

Baseline demographics and disease characteristics are listed in Table 1.

Table 1 Baseline Patient Characteristics

Characteristic	Value, N (%)
Age (years), median (range)	76 (72-82)
Performance Status	
0	6 (24)
1	18 (72)
2	1 (4)
Gleason Score	
6	2/20 (10)
7	5/20 (25)
8-10	13/20 (65)
Unknown/not determined	5
Time to development of castration resistance (months), median (range)	19.5 (11-24)
Duration on AAP before study entry (months), median (range)	12.1 (8-19)
Extent of Metastatic Disease	
Bone metastases	23 (92)
Lymph node metastases	12 (48)
PSA (ng/mL), median (range)	36 (5-1411)
Glucose (mmol/L), median (range)	5.7 (4.3-7.9)
Hemoglobin (g/L), median (range)	135 (98-155)
Creatinine (μmol/L), median (range)	73 (51-105)

Abbreviations: PSA = prostate-specific antigen; AAP = abiraterone acetate prednisone.

Efficacy

Twenty-four of 25 patients stopped treatment because of disease progression. The primary end point, PFS12, was reached in 12% (3 of 25 patients) (95% confidence interval, 3-31). Most patients had PSA progression; almost half had radiographic progression, but only one patient had symptomatic progression. Details on treatment response at 12 weeks are listed in Table 2. Median PFS was 9 weeks (interquartile range [IQR] = 7-11). No patient was free of progression at 24 weeks. The median overall survival was 20.7 months (IQR = 14-23). With regard to PSA response, only 3 patients demonstrated a minor and transient decrease in PSA. No patient experienced a PSA response of > 30% at any time point. Waterfall plots for PSA change from baseline are displayed in Figure 1.

Safety

Eleven (44%) of 25 patients had grade 1 and 2 patients each grade 2 (8%) or grade 3 (8%) gastrointestinal toxicity (nausea, diarrhea, loss of appetite). One patient discontinued treatment at week 5 as a result of intolerable grade 3 diarrhea. Details on adverse events are listed in Table 3. No dose reductions of abiraterone, prednisone, or metformin were recorded.

Metabolic Analyses

The median BMI at baseline was 25.7 kg/m^2 (IQR = 23.7-28.4); 13 patients (52%) had a BMI of 25 to 29.9 kg/m^2, indicating overweight; and 4 patients (16%) had a BMI of $\geq$ 30 kg/m^2, indicating obesity. The median baseline HbA1c was 6.0% (IQR = 5.7-6.0%; normal = < 6.5%). The baseline fasting glucose was 4.4 mmol/L (IQR = 3.7-5.7 mmol/L; normal: 3.9-6.1 mmol/L), and the baseline insulin was 7.8 mU/L (IQR = 4.8-11.4 mU/L).

Glucose, insulin, HbA1c, C-peptide, insulin-like growth factor 1, and BMI levels did not change from baseline to 12 weeks (data not shown). Furthermore, no improvement of glucose tolerance while receiving metformin was observed at 12 weeks (Wilcoxon signed-rank test P = .97).

Discussion

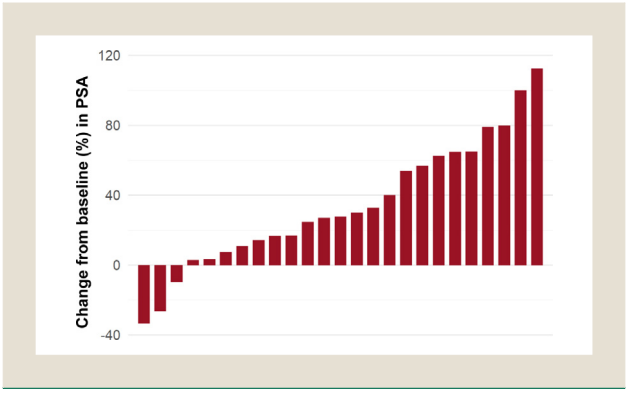
To our knowledge, this is the first prospective clinical trial to test the addition of metformin to the testosterone synthesis inhibitor abiraterone in patients with mCRPC. Hypothesizing that metformin might be capable of restoring ASI sensitivity, we chose to add metformin to patients experiencing PSA progression while receiving abiraterone treatment. PSA progression only is a good window of opportunity to test the impact of potentially sensitivity-restoring drugs because no immediate change of systemic treatment was necessary in this clinical situation according to current consensus.[1] Our cohort included asymptomatic patients with lymph node

Table 2 Details of Treatment Response at 12 Weeks (N = 25)

Response Assessment	Response	Stabilization, N (%)	Progression, N (%)
PSA	0	3 (12)	22 (88)
Radiographic	0	14 (56)	11 (44)
Clinical	0	24 (96)	1 (4)

Abbreviation: PSA = prostate-specific antigen.

Figure 1 Waterfall Plot for Best PSA Response (N = 25)



Abbreviation: PSA = prostate-specific antigen.

and/or bone metastases who had received abiraterone therapy for a median of 12 months before study entry. We found that the addition of metformin to continued abiraterone had no meaningful impact on any of the assessed relevant clinical variables and did not result in prolongation of PFS or PSA response. Apart from the lack of clinical efficacy, we observed a higher-than-expected toxicity with the combination of metformin and abiraterone. We were surprised to find 60% of patients experiencing grade 1, grade 2, or even grade 3 gastrointestinal toxicity, which can be bothersome for patients.

The negative outcome of our clinical study was unexpected because the preclinical evidence that metformin might be an active drug in castration-resistant prostate cancer has increased over the past years. Two in vitro and in vivo studies suggested that the addition of metformin to cell lines and xenograft models refractory to the ASI enzalutamide could restore sensitivity. One experiment focused on autophagy modulation through metformin leading to impaired cell survival.[24] The other study demonstrated that metformin was capable of reversing resistance to enzalutamide through inhibition of epithelial to mesenchymal transition targeting the TGF-β1/STAT3 axis.[25] Apart from acting on these two possible

Table 3 Details of Adverse Events (N = 25)

Adverse Event	N (%)
Nausea	
Grade 1	4 (16)
Grade 2	1 (4)
Diarrhea	
Grade 1	3 (12)
Grade 2	1 (4)
Grade 3	1 (4)
Loss of Appetite	
Grade 3	1 (4)
Constipation	
Grade 1	3 (12)
Anemia	
Grade 1	1 (4)

Adverse events were defined by National Cancer Institute Common Terminology Criteria for Adverse Events v.4.0.

resistance mechanisms, several other antineoplastic properties attributed to metformin that might possibly reverse ASI resistance have been described[26]: abrogation of AR up-regulation, inhibition of androgen-dependent insulin-like growth factor 1R up-regulation, and decrease of c-MYC resulting in AR reduction. Even down-regulation of AR-V7 splice variant associated with ASI resistance has been demonstrated.[27]

Possible explanations for the failure of metformin to reverse ASI resistance are the different modes of action of enzalutamide and abiraterone, and the need to add steroids to abiraterone, which might abrogate the effect of metformin. Induction of glucocorticoid receptor expression was identified as a common feature of drug-resistant tumors in a credentialed preclinical model, a finding also confirmed in patient samples. Glucocorticoid receptor substituted for the AR to activate a similar but distinguishable set of target genes.[28]

Most currently available data on metformin and its efficacy as antineoplastic agent are based on either retrospective epidemiologic analyses or preclinical experiments. Only one clinical trial has been published to date in prostate cancer showing some influence on PSA for patients with slowly progressive low-volume mCRPC (2 of 44 patients with PSA > 50% response and 36% PFS12).[19] A recently reported study in breast cancer patients failed to demonstrate enhancement of the efficacy of aromatase inhibitors by metformin.[29] These modest results of the currently published prospective clinical trials are in line with the negative outcome of our study and raise questions regarding the impact of metformin as a clinically relevant antineoplastic drug. Several trials in different cancer types are ongoing that will help elucidate the place of metformin in cancer treatment in the future. Metformin is currently tested in many different disease stages in prostate cancer. One of the largest trials involving metformin is the Stampede study, where metformin is added to ADT in patients with castration-sensitive locally advanced or metastatic patients.[30]

Metformin is also expected to mitigate the side effects of hormone treatment, but interestingly, we did not find an effect on glucose levels and glucose tolerance. However, these studies were limited by small sample sizes.

Some weaknesses of our study must be discussed. We did not perform a randomized study, and hence it remains unclear if the impact of metformin is indeed negligible. However, our results do mirror the findings in the registration trial COU-AA-302, in which patients with PSA progression continued to receive therapy with abiraterone alone, with a median time to radiographic progression of approximately 5 months and a time to symptomatic progression of over 15 months.[4] This is similar to our results, with the addition of metformin suggesting no apparent impact. Another obvious weakness is the small number of patients in our pilot study, which might have resulted in an underestimation of the efficacy of metformin. In view of the fact that the primary end point of PFS12 was only reached by 12% of patients, and no patient experienced a PSA response of > 30% decline at any time point, it appears unlikely that a larger number of patients would have demonstrated more encouraging results. Moreover, the patient group was somewhat heterogenous, which is highlighted by the large difference of PSA value at baseline. We might therefore have missed a possible benefit in patients with lower tumor burden. Our findings are strengthened by the study population corresponding very well to the population

in the registration phase 3 trial COU-AA-302 (asymptomatic or mildly symptomatic, no visceral metastases, PSA progression while receiving abiraterone therapy after 11.1 months), the fact that the patients were recruited in only 3 experienced centers, and the fact that patients continued to receive the study drug despite rising PSA levels until the primary end point of PFS12 was reached in order not to miss any late responses.

Conclusion

On the basis of our results, we conclude that the addition of metformin to abiraterone for mCRPC is not beneficial in cases of PSA progression. Moreover, despite the nonoverlapping toxicity profile of abiraterone and metformin as well as generally good tolerance, we observed a higher-than-expected gastrointestinal toxicity attributed to metformin. Whether the addition of metformin might be beneficial in combination with enzalutamide is unclear and is currently under investigation in clinical trials.

Given the lack of any meaningful response, this combination should not be further investigated or used outside of trials. Our results suggest that the impact of short-term metformin treatment for patients with mCRPC is likely very limited. Whether an earlier start or a prolonged treatment with metformin is more beneficial remains to be proven.

Clinical Practice Points

- Abiraterone has become one of the preferred first-line hormone treatments in mCRPC for patients with no or mild symptoms. The combined blockade of the androgen and the mammalian target of rapamycin (mTOR) pathway might restore sensitivity to antiandrogen therapy.
- We hypothesized that the effects of metformin leading to mTOR inhibition could reverse resistance to abiraterone and prolong time to progression while receiving abiraterone therapy.
- The addition of metformin to abiraterone for mCRPC is not beneficial in cases of PSA progression. Despite good preclinical evidence, we could not demonstrate that it had the potential to reverse resistance mechanisms to ASIs.
- Despite the nonoverlapping toxicity profiles of abiraterone and metformin, and generally good tolerance, we observed a higher-than-expected gastrointestinal toxicity attributed to metformin. Given the lack of any meaningful response, this combination should not be further investigated or used outside of trials.
- The impact of short-term metformin treatment for patients with mCRPC is likely very limited. Whether an earlier start or a longer treatment with metformin is more beneficial remains to be proven.

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Disclosure

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