The landscape has changed dramatically for treatment of castrate-resistant prostate cancer (CRPC) in the last 4 yr. Further androgen-axis manipulation with abiraterone and enzalutamide, second-line chemotherapy with cabazitaxel, and immune therapy with sipuleucel-T all have shown improvements in overall survival ranging from 2.5 mo to 5 mo. Couple these advancements with new bone-targeted agents, and the outlook for patients with advanced prostate cancer (PCa) has been improved dramatically.

However, survival improvements observed in each trial come at substantial cost. It is tempting to conclude we will see additive survival benefits when we sequentially administer these therapies, but, truthfully, the estimated survival for modern-era CRPC patients is unknown. We do not yet know the correct sequence or what, if any, combinations will yield synergy, and we have much work to do in developing biomarkers predicting who will respond best to which therapy.

While we await answers to these questions and the next wave of new drug developments, why not think inside the box of old, common, generic medications?

1. **Enter metformin**

In this month’s issue of *European Urology*, Rothermundt and colleagues describe their phase 2 trial of metformin in 44 nondiabetic men with minimally symptomatic, metastatic CRPC who had not received chemotherapy [1]. This is the same metformin, a biguanide, that is the most commonly prescribed oral hypoglycemic agent worldwide. It inhibits hepatic gluconeogenesis, stimulates glucose uptake, and reduces insulin resistance and mortality [2].

Rothermundt et al. observed that 36% of CRPC patients were progression-free at 3 mo, 9% were progression-free at 6 mo, and median progression-free survival was 2.8 mo. Of those who progressed by 3 mo, nearly half were categorized as such based on increased prostate-specific antigen (PSA) level alone. In total, 5% of patients had a $\geq 50\%$ PSA response. More than half had a prolongation of their PSA doubling time, with the median extending from 88 d to 111 d (a 26% relative slowing). The drug was very well tolerated with no grade 3/4 adverse events.

How do we interpret these results? At first blush, these data seem encouraging in a disease state that invariably progresses using a drug designed and approved for a completely different indication. Though the sample size was small, the study was powered appropriately and achieved their phase 2 efficacy goal. However, without a control comparator group, it is difficult to truly understand the activity of metformin. We are left to contextualize with other studies, which can be precarious with different trial populations.

On one hand, the data pale in comparison with data on abiraterone or enzalutamide in the chemotherapy-naïve setting. For example, patients receiving abiraterone in the COU-AA-302 study remained free of PSA progression for 11 mo and radiographic progression for 16.5 mo, on average; nearly two-thirds achieved a $\geq 50\%$ decline in PSA level [3]. Though the data from the Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-naïve Patients with Progressive Metastatic Prostate Cancer (PREVAIL) have yet been


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published, the preliminary press release suggests similar results for enzalutamide [4]. However, it may be unfair to compare metformin to these blockbuster drugs designed specifically for CRPC.

Interestingly, even the prednisone-only control arm of COU-AA-302 remained PSA progression-free for 5.6 mo and radiographic progression-free for 8.3 mo, and 24% had >50% decline in PSA level. Until the PREVAIL results are published, we will not have a modern-era placebo group for comparison, though preliminary radiographic progression-free survival was 3.9 mo for this group.

2. Why not metformin?

The signal observed in this phase 2 trial, while modest, is encouraging. Though the true activity of metformin in CRPC remains unknown, there are several reasons why studying it further makes sense.

2.1. Cost

For the small, yet significant improvements in overall survival seen with the recent CRPC therapies, the cost to patients and/or health-care systems is large. The approximate cost (in US dollars) of a typical course of docetaxel is $24,000; for abiraterone, $40,000; enzalutamide, $60,000; cabazitaxel, $56,000; and sipuleucel-T $93,000. By contrast, generic metformin at 1000 mg twice daily for similar treatment duration would range from $700 to $1200.

2.2. Side effects

Metformin has a favorable safety profile compared to abiraterone, which can cause fluid retention, edema, hypertension, and hypokalemia [3,5]; enzalutamide, for which the small increase in seizure risk has prompted precautions on labels [6]; cabazitaxel, which has significant hematologic side effects [7]; and sipuleucel-T, which commonly induces fever, chills, headache, and myalgias [8].

2.3. Biological and clinical rationale

Metformin inhibits in vitro and xenograft growth of several PCa cell lines [9]. It is hypothesized that metformin acts through both insulin-dependent and insulin-independent mechanisms. Rothermundt et al. highlight the insulin-dependent mechanisms. The insulin-independent mechanisms involve metformin activating adenosine monophosphate (AMP)-activated protein kinase (AMPK), which subsequently inhibits mammalian target of rapamycin (mTOR) signaling [10]. Metformin may also directly modify expression of tumor suppressor genes and/or oncogenes such as c-MYC, which has been implicated in PCa initiation and progression [11].

Recent evidence suggests activation of AMPK leads to downregulation of androgen-receptor (AR) levels. Interestingly, decreased AR activity reciprocally enhances AMPK activation, while increased AR activity inhibits the apoptotic effects of metformin AMPK activation [12]. Thus, using metformin along with androgen deprivation therapy (ADT) may maximize metformin activity, but waiting until CRPC develops, when AR signaling is increased (through amplification, mutations, and intracellular androgen stimulation), may hamper metformin’s ability to inhibit growth. This suggests we should also look at metformin earlier in the disease process in patients starting ADT but not yet castrate resistant.

Despite exciting in vitro and animal evidence of metformin’s antineoplastic activity, the clinical evidence has been more confusing. Metformin use does not appear associated with a reduced risk for PCa development or a reduced risk for recurrence after surgery [13,14]. However, there is strong suggestion it inhibits development of CRPC and death from PCa by 25% to 45% [15–17].

3. Conclusions and future directions

Rothermundt and colleagues are to be congratulated for taking metformin to clinical trial in CRPC. The results, while not blockbuster, are encouraging and we should push forward.

And why not? Metformin is a drug accepted worldwide; it has proven safety over decades; physicians are comfortable prescribing it; it is inexpensive relative to other therapies for CRPC; it counteracts side effects of ADT, such as insulin insensitivity, hyperinsulinemia, and diabetes; and it has mechanisms targeting pathways of tumor growth. Most important for CRPC patients, those who do not die from PCa are likely to die from cardiac causes, thus metformin may reduce the risk of cardiac and PCa death.

Moving forward, a larger controlled trial of metformin in early CRPC is warranted and likely feasible. We should strive to identify a pharmacogenetic marker predictive of response/nonresponse. Interactions with enzalutamide and abiraterone should also be explored, since there is rationale for synergy. Finally, we need to look at more than just PSA and clinical progression end points, as the ability of metformin to reduce hyperinsulinemia and hyperglycemia could prolong overall survival, even if not impressively reducing progression-free survival.

Conflicts of interest: The author has nothing to disclose.

References

[4] Medivation and Astellas announce the phase 3 PREVAIL trial of enzalutamide meets both co-primary endpoints of overall survival and radiographic progression-free survival in chemotherapy-naive patients with advanced prostate cancer. Astellas
Platinum Priority


The Stage Is Set for Metformin

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1. Prologue

The “most fruitful basis of the discovery of a new drug is to start with an old drug,” said Sir James W. Black, 1988 Nobel laureate in medicine.

2. Act 1: Monotherapy

Metformin has been discussed as anticancer drug for some time [1]. The preclinical rationale for metformin use in prostate cancer (PCa) is discussed in the editorial [2]: direct actions of the drug on cancer cells and indirect effects related to changes on host hormone environment and metabolism. The former mechanism requires achievement of adequate drug concentrations in the prostate. The latter involves insulin and/or insulin growth factor 1 (IGF-1) signaling.

The IGF-1 receptor (IGF-1R) is a widely expressed receptor tyrosine kinase and activates the MAPK and PI3K/Akt signaling pathways [3]. Preoperative figitumumab, an IGF-1R antibody, has been reported to decrease IGF-1R and androgen receptor (AR) expression in prostatectomy samples and is associated with declines in prostate-specific antigen (PSA) levels [4]. In an earlier trial, the somatostatin analog octreotide acetate, which has been shown to reduce IGF-1 production, was assessed in patients with nonmetastatic castration-resistant PCa (CRPC). Circulating IGF-1 and insulin-like growth factor binding protein 3 were suppressed. However, in contrast to our study [5], the biochemical effect of octreotide was not mirrored in PSA or objective responses [6]. The paleness of the metformin effect in CRPC could be explained by the fact that PCa cells may be more dependent on IGF signaling prior to development of castration resistance, yet the story is more complex: Crosstalk between the AR and PI3K pathways has been shown preclinically, with PI3K pathway inhibition resulting in activation of AR through HER2/HER3 signaling and AR inhibition activating Akt [7].

3. Act 2: Combination treatment

Combination of metformin with abiraterone acetate or enzalutamide, as proposed in the editorial [2], is a plausible and attractive next step. The mechanisms leading to resistance against abiraterone are not, as yet, completely understood. Resistant tumor cells probably develop escape mechanisms with activation of pathways independent of


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