

PCa Commentary #96.2: Metformin

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METFORMIN:

Your patient may ask, “Doctor, should I be taking Metformin for my prostate cancer?”

Clinical trials have not yet given an unambiguous answer to this important question. Currently the conundrum is, why does this drug look so promising in laboratory studies, and yet current clinical trials have produced such varied and contradictory results? This issue does not lack for academic research pursuing the mechanism of action for the anti-cancer effect of this common drug.

Metformin has been in use as a standard treatment for type 2 diabetes for more than 60 years and has compiled an excellent safety record, and, importantly for persons taking the drug who do not have diabetes, metformin does not cause low blood sugar. The side effects are essentially a low risk of diarrhea or G.I. upset. However, the research into the anti-neoplastic effect of this commonly used drug is just beginning to mature.

BASIC SCIENCE STUDIES:

The earliest research studies on metformin focused on men with Type 2 diabetes taking the drug v. diabetic men who were non-users. The results suggested that metformin was associated with a lower incidence of prostate cancer and a slowing of disease progression. These findings stimulated the search for the mechanism(s) underlying these observations.

Since this early research, multiple studies have found that the apparent anti-cancer benefits of metformin result from interference in multiple cellular signaling pathways quite different from those relevant to diabetic control. The many pathways involved (and their names are arcane) are quite unfamiliar to non-molecular biologists, but they all converge in repressing prostate cancer viability and enhancing cell death, retarding the progression of the cell cycle — hence slowing prostate cancer growth, inhibiting cellular invasion and migration, and inhibiting disease progression by interfering with tumor suppressors.

A crucial transition point for non-invasive prostate cancer, i.e., Gleason score 6, is oncogene activation of the epithelial-mesenchymal transition (EMT) which changes benign cellular behavior to invasiveness and leads into castration-resistant prostate cancer. Some studies show that metformin inhibits this transition.

A potential unifying concept has been offered by Wang *et al.* "Metformin Represses Androgen-Dependent and Androgen-Independent Prostate Cancer by Targeting Androgen Receptor, (*The Prostate*, 75, 2015). Their query was whether metformin reduced the abundance of androgen receptors (AR) produced in a cell, thereby decreasing the pivotal target for androgen activation and the attendant cellular proliferation. Their conclusion carried a practical message:

"Metformin represses prostate cancer cell viability and enhances apoptosis [cellular death] by targeting the AR signaling pathway. Combinations of metformin and other anti-AR agents

[i.e., Casodex, Xtandi, and Zytiga] pose a promising therapeutic approach for treatment for

prostate cancers, especially castration-resistant disease, with high efficiency and low toxicity."

When metformin was combined with bicalutamide [Casodex] the effect was even stronger than with metformin alone. This benefit from down-regulating of AR production also applied to the subversive cell growth promoting splice variant AR-V7.

Further research on metformin digs deeper into cellular biology — metformin's effect on stem cells:

Basic research studies suggest metformin interferes with the process of stem cell mitochondrial energy production (i.e. ATP creation) with a consequent weakening of cellular vitality. Klotz *et al.* ("Metformin and prostate cancer stem cells: a novel therapeutic target, "*Prostate Cancer and Prostatic Diseases*. 2015) reviewed the inferred importance of the cancer stem cell (CSC) as a principle source of resistance to both chemotherapy and radiotherapy, pointing out that this cell is impervious to damage from both modalities. This resistance is thought to be the genesis of cancer recurrence after treatment.

The authors postulate: "Metformin could be used to exploit this metabolic weakness in CSCs. This would increase CSC sensitivity to conventional cancer therapies, circumventing treatment resistance and enhancing treatment efficacy." That is to say, metformin could sensitize a cell to radiation and chemotherapy damage.

CLINICAL STUDIES:

Why hasn't the abundance of these positive features resulted in unequivocal benefits in prevention of prostate cancer, delay in cancer recurrence after primary therapy and the development of metastatic cancer? Why hasn't the conversion to castration-resistant prostate cancer (CRPC) been slowed, and, most importantly, why no survival benefit? There seems to be as many studies affirming benefit as denying it — some well done, but based on too small samples; some with inappropriate patient selection or stratification.

One enthusiast convinced of metformin's benefit is Dr. Charles Myers, a prostate cancer guru sought for advice and consultation by many patients. He endorses metformin at the standard anti-diabetic dose of 1000 mg twice daily in all phases of the disease. He was particularly impressed by a Swiss study that he felt was very well done: "Metformin in Chemotherapy-naive Castration-resistant Prostate Cancer: A Metacenter Phase 2 Trial," by Rothermundt *et al.*, *European Urology*. Jan 2014. The study focused on "the effect of treatment on progression-free survival (PFS) and PSA doubling time (PSA DT). This small study was based on only 44 patients. It found that "thirty-six percent of patients were progression-free at 12 wk, 9.1% were progression-free at 24 wk, and ... in 23 patients (52.3%) it reported a [modest] prolongation of PSA doubling time after starting metformin.

[Note: The protocols listed below all use metformin at 850 mg twice daily.]

A comprehensive and informative meta-analysis reviewing the conflicting evidence regarding metformin's role in prostate cancer was reported Ravel *et al.*, in *Prostate Cancer Prostatic Diseases*, Jun 2015: "Impact of metformin on clinical outcomes among men with prostate cancer: a systematic review and meta-analysis."

The findings: Based on 21 studies (out of 230) accepted for analysis, the review reported that metformin usage was associated with a 9% decrease in prostate cancer incidence; an 18% reduction in disease progression (i.e. biochemical recurrence); and "mixed findings on the use of metformin and the risk of CRPC." No significant reduction was found in the development of metastases, in prostate cancer specific mortality, or in all-causes mortality.

What to do? It is understandable that a man in the thick of his fight with prostate cancer would be inclined to opt for the potential benefits of metformin, especially since the drug has an excellent safety profile and is (currently) inexpensive. An 18% chance to delay the development of biochemical recurrence is very appealing. However, the substantive "proof of the pudding" will come from the several ongoing protocols addressing metformin in various phases of the disease.

Caveat: Nearly everyone agrees that validation from forthcoming protocol information is required before metformin can assume an accepted role in prostate cancer management.

What is being studied and what guidance might be learned when these protocols are completed?

- A Phase II study to determine if Metformin can increase prostate specific antigen doubling time in men having failed surgery or radiation and who have a high risk for recurrence. NCT02176161
- A study to determine if metformin in addition to ADT compared to ADT alone can ameliorate the metabolic consequences of ADT in men with recurrent or metastatic cancer, and to evaluate comparative rates of disease progression. NCT1620593
- A randomized, Phase II study evaluating the combination of metformin with docetaxel (Taxotere) versus Taxotere alone as treatment for metastatic CRPC. NCT01796028

- The Metformin Active Surveillance Trial “aims to see if metformin can delay the time to progression in men with low risk prostate cancer compared to a placebo.” NCT01864096
- A study “to assess the impact of the addition of metformin to abiraterone (pre-docetaxel) on survival in CRPC patients with metastatic prostate cancer.” NCT01677897
- A 6 month study to determine if metformin use in men with a rising PSA after primary therapy will slow PSA progression by 20% or more. This is the first trial to utilize a new study design to shift from the current paradigm of “bringing patients to trials” to “bringing trials to patients.” The enrollment visit is on-site but all follow-up is conducted by a secured telemonitoring system. NCT02376166

BOTTOM LINE:

Metformin is a notably safe drug which, in preliminary trials, has demonstrated an 18% decrease in the risk of biochemical progression (i.e. PSA rise) of prostate cancer after primary treatment, and may delay the development of CRPC. Although promising, these findings need validation. Six clinical trials are in progress to assess metformin’s performance in various phases of the disease.