Repurposing To Fight Cancer: The Metformin–Prostate Cancer Connection

By Anna Azvolinsky

Already recommended as a first-line therapy for diabetic men diagnosed with prostate cancer, metformin is one of the most widely prescribed drugs in the world. Diabetics use it every day to control blood sugar. Oncology may offer another use for the drug. Results from retrospective studies have been mixed depending on whether the study examined prevention or cancer outcomes. But on the basis of recent evidence, researchers suggest that it may be time to conduct prospective trials of metformin to test its effectiveness on prostate cancer progression.

In one study, diabetic men with prostate cancer who took metformin were less likely to die from their cancer and lived statistically significantly longer irrespective of prostate cancer treatment received (*J. Clin. Oncol.* 2013;31:3069–75). The same analysis, by Neil Fleshner, M.D., of the Princess Margaret Hospital in Toronto, Canada, showed a 24% decrease in death from prostate cancer for each cumulative 6 months of treatment with metformin. The almost-3,900-patient retrospective study showed that this benefit was specific to metformin: Other diabetes drugs did not have the same effect.

This is one of many retrospective studies linking metformin with prostate cancer, but not all are positive. Another population study, also by Fleshner, showed that diabetic men taking metformin did not have a lower incidence of prostate cancer (*J. Natl. Cancer Inst.* 2013;105:1123–31).

The different origins of indolent and aggressive prostate cancer may account for the dissimilar results for incidence and disease progression.

"The data suggest that metformin use may affect the aggressive type," said David Margel, M.D., Ph.D., of the University of Toronto, Canada, and first author of both described studies. Meir J. Stampfer, M.D., an epidemiologist at the Harvard School of Public Health in Boston, agrees.

"Studies attempting to identify risk factors for overall prostate cancer incidence often produce conflicting results as a consequence of that difference," Stampfer wrote with coauthor Kathryn L. Penney, Sc.D., in an accompanying editorial (*J. Clin. Oncol.* 2013;31:3054–5).

Stampfer supports a large, long-term randomized metformin trial in men with localized prostate cancer, regardless of whether they have diabetes.

"There is a genuine question here that requires a randomized trial," Stampfer said.

Definitive Data Still Lacking

Metformin is an inexpensive generic drug that is typically the first line of treatment for someone newly diagnosed with type II (adult-onset) diabetes. The drug was synthesized in the 1920s and has been used in Europe and Canada since the 1970s. The U.S. Food and Drug Administration approved it in 1994.

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Interest in metformin as an anticancer agent began when diabetes specialists noticed that patients taking metformin had a lower incidence of cancer than that of other diabetes patients. Retrospective studies followed, many showing that diabetics taking metformin were less likely to be diagnosed with cancer and that those so diagnosed were less likely to die.

"This finding provided a strong impetus for further investigation," said Michael Pollak, M.D., a metformin researcher at McGill University in Montreal, Canada. "It would have been almost malpractice not to investigate this." One meta-analysis of six such studies showed a statistically significant reduction in relative risk of all-cancer incidence by 33% (*PLoS One* 2012;7:e33411).

Michael Pollak, M.D.

But in the last 2 years, the pharmacoepidemiology data have received more scrutiny. Experts have questioned the retrospective analyses, highlighting inconsistent definitions of a metformin user that probably exaggerate the drug's potential antitumor activity (*Diabetes Care* 2012;35:2665–73). Another issue, according to molecular biologist Kevin Struhl, Ph.D., of Harvard Medical School in Boston, is that whether the data on diabetics apply to the general population is unclear.

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According to Pollak, the available results need to be regarded as hypothesis generating: much remains to be understood about metformin's anticancer properties.

Laboratory Evidence

Many researchers, including Pollak, have used cell lines and mouse models to study

how metformin could either prevent tumor initiation or inhibit tumor growth. Metformin may exert its anticancer effects directly on prostate tissue or indirectly by modulating insulin levels and metabolism. In diabetics, metformin decreases glucose production in the liver, lowering serum glucose levels, which can also affect tumor growth. Its direct effect may be to decrease proliferation and inhibit tissue inflammation.

Several studies suggest that metformin could work best in combination with other agents, including chemotherapy. Sarah-Maria Fendt, Ph.D., of the Vesalius Research Center in Belgium, showed that metformin affects prostate cancer cells by increasing their dependence on glutamine metabolism (*Cancer Res.* 2013;73:1–10). The study suggests that the combination of metformin with a glutaminase inhibitor should be tested in prostate cancer.

Using xenografts, Struhl showed that metformin combined with chemotherapy can block tumor growth and prevent recurrence of prostate cancer in mice, partly by blocking inflammatory pathways (*Proc. Natl. Acid. Sci. USA* 2013;110:972–7). The mouse data also suggest that chemotherapy may be effective at a fraction of the standard dose when combined with metformin and the effect could be general for many types of cancer.

"A lot of good data have been generated, but whether this will work in people is the question," said Struhl, who is also concerned that clinicians who run trials are not readily aware of preclinical research or dismiss laboratory evidence as an artificial system. "There may be clinical trials that are not being done in the best way from a science evidence point of view," Struhl said.

Repurposing a Generic Drug

Metformin appears ideal: well tolerated, long-term safety record, and inexpensive. But unlike a proprietary compound developed by a company, metformin trials have not followed the typical clinical development scheme because the drug is already accessible to clinicians.

A lack of coordination by one company and low cost of the drug have resulted in hundreds of clinical trials, large and small, testing whether metformin can either help treat or prevent not only prostate cancer but also breast, endometrial, and pancreatic cancer, among others. Most such trials are testing metformin at its antidiabetes dose, which is backed by safety data.

"This situation is a mixed blessing," Pollak said. "The lack of coordination can result in trial duplication and uneven quality, but it also creates an even playing field for anyone to do a trial."

The largest randomized, prospective metformin trial, funded by the National Cancer Institute, is now testing metformin as an adjuvant therapy to prevent breast cancer recurrence. The 6-year trial has enrolled more than 3,500 patients. Whether a similar government-funded trial in prostate cancer will begin soon is not yet clear. The trial Stampfer advocates would address how metformin affects prostate cancer mortality. Because of that cancer's slow clinical progression, such a trial would require long-term follow up, many patients, and much funding.

"Still, this is a trial worth doing," Stampfer said. If results are positive, metformin would be readily affordable for patients.

From Observational Studies to Trials

Metformin is already recommended as a first-line therapy for diabetic men diagnosed with prostate cancer. Randomized trials and a better understanding of how metformin works may also identify patients more likely to benefit from the drug, Margel said.

On the basis of their results, Fleshner is leading the Metformin Active Surveillance Trial (MAST) in Canada. The randomized, placebo-controlled trial will evaluate whether metformin can delay time to progression for men with low-risk, early-stage prostate cancer. He is also considering a trial to test metformin in advanced prostate cancer, probably in combination with an available therapy.

Many other questions remain: Can metformin be more effective in combination with chemotherapy or other cancer treatment in patients? Could other cancer types benefit from metformin treatment? Is the antidiabetes dose of metformin actually the best antitumor dose? Many possibilities exist for new trials.

There is also the possibility that other members of the class of biguinide drugs to which metformin belongs may have anticancer activity. "The more general question of whether any dose of a biguinide has anti-neoplastic activity has not yet been addressed" said Pollak.

"It's an exciting time, but we have to be cautious. There is a good base of laboratory science and epidemiological data that says we should do trials [with metformin]," Fleisher said. "But I am a skeptic until proven otherwise. I think we should hold our enthusiasm until we get the results."

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Navigating Cancer Treatment

By Kurt Ullman

In the 1990s Harold P. Freeman, M.D., noticed that most women he saw at Harlem Hospital in New York came to his clinic with late-stage breast cancer. When he looked further, many women were not being diagnosed because of barriers to care such as lack of health insurance and confusion about how and why they should get mammograms.