

Use of Metformin as Adjunctive Chemotherapy in Patients with Cancer

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The American Diabetes Association (ADA) issued a consensus report in 2010 addressing diabetes and cancer.¹ In this review, metformin was noted to have numerous effects on cancer, specifically breast cancer cell lines. In laboratory experiments, metformin inhibited cell proliferation and caused partial cell cycle arrest in some cancer cells. Metformin activates adenosine-monophosphate (AMP)-activated protein kinase (AMPK), which in turn inhibits growth of cancer cells because it inhibits protein synthesis. Studies in mice injected with lung carcinoma cells showed the antineoplastic effect of metformin was greater in subjects on a high-energy diet than those on a control diet, as measured by tumor size.² This indicates the insulin lowering action of metformin may play a role in its anti-cancer actions.

A review by Rattan et al delves into the mechanism by which metformin slows tumor growth.⁶ As previously noted, metformin activates AMPK, which leads to downstream effects including inhibition of the mammalian target of rapamycin (mTOR), activation of p53 and p21 (both of which result in cell cycle arrest), inhibition of sterol and lipid synthesis pathways, and a systemic effect that reduces circulating levels of growth factors such as insulin, leptin, and insulin-like growth factor (IGF). In vitro studies have shown metformin to inhibit the growth of numerous types of cancer cells, including glioma, breast, pancreatic, colon, renal, ovarian, endometrial, lung, and prostate. Metformin may also be effective against metastasis. There are currently 2 theories on how metastases arise: either by epithelial to mesenchymal transition or via cancer stem cells. Metformin has been shown in vitro to inhibit both of these, via similar mechanisms as described before. These antineoplastic properties have made metformin the subject of numerous trials, though many are still in their early stages.

Per the ADA consensus report, several observational studies show that patients with diabetes, when treated with metformin compared to other agents, such as sulfonylureas and insulin, have a lower risk of cancer or cancer mortality.¹ These observational studies, however, are likely confounded; the patients taking metformin were generally healthier and had a shorter history of diabetes than those on other antidiabetic therapies. The ADA notes that associations of specific antidiabetic agents with cancer risk are likely confounded by other factors, including body weight, hyperglycemia, hyperinsulinemia, drug indication, and the complexity of diabetes, though early evidence suggests metformin is associated with a lower risk of cancer compared to other therapies, such as sulfonylureas and insulin. Further research is needed to clarify the role of metformin and cancer risk.

A meta-analysis by Noto et al examined cancer risk in patients with diabetes taking metformin.³ They included studies involving patients with type 2 diabetes who received metformin, both randomized controlled trials (RCTs) with ≥ 1 year of follow-up and observation studies of any duration. Pooled risk ratios (RRs) were used for cancer incidence and cancer mortality. Ten studies (2 RCTs, 6 cohort studies, 2 case-control studies) including 21,195 patients met criteria and were selected to evaluate cancer incidence while 6 studies (4 cohort studies, 2 RCTs) including 210,892 patients were used to evaluate cancer mortality. The RR for all-cancer

incidence was 0.68 (95% confidence interval [CI] 0.53 to 0.88) and 0.66 (95% CI 0.49 to 0.88) for cancer mortality. Significant risk reductions were found for colorectum (RR 0.68, 95% CI 0.53 to 0.88), liver (RR 0.20, 95% CI 0.07 to 0.59), and lung cancer (RR 0.67, 95% CI 0.45 to 0.99). The authors noted that there were significant differences among the types of studies. Evaluating heterogeneity among the different study types, significant variation was observed among the observational cohort studies but not the RCTs or case-control studies. In addition, the RCTs showed no benefit of metformin on cancer incidence and cancer mortality, while the observational studies demonstrated otherwise. Interestingly, the duration of the observational studies was not reported.

Another meta-analysis examined cancer mortality associated with metformin and other therapies.^{4,5} Stevens et al evaluated RCTs of minimum duration 1 year in which ≥ 500 patients without preexisting cancer were given metformin. Thirteen trials were included in the analysis, comprising 66,447 person-years of follow-up. The pooled RR for all-cause mortality was 0.99 (95% CI 0.83 to 1.17). Of note, not all trials included in the meta-analysis were specifically designed to evaluate cancer mortality. Also, though the authors only included trials of 1 year or more, this is a relatively short time period to evaluate patients for cancer mortality.

Jiralerspong et al investigated the role of metformin in early-stage breast cancer patients receiving neoadjuvant chemotherapy.⁷ Patients with diabetes taking metformin were compared to patients with diabetes not taking metformin and patients without diabetes. The primary endpoint was the effect of metformin on growth of tumor cells, as measured by pathologic complete response (pCR). pCR was significantly higher in patients with diabetes taking metformin (n=68) compared to those not taking metformin (n=87), at 24% vs. 8%, respectively (p=0.007). Interestingly, patients with diabetes taking metformin had a higher pCR than patients without diabetes (n=2,374), though not significantly (24% vs 16%, p= 0.10) In this study, a multivariate logistic regression model found that metformin was independently predictive of pCR (odds ratio 2.95, 95% CI 1.07 to 8.17) after adjustment for age, stage of cancer, body mass index, diabetes, grade, receptor status, and neoadjuvant taxane use.

In contrast, Bayraktar et al examined metformin use in patients receiving adjuvant chemotherapy for triple negative breast cancer.⁸ This study also evaluated patients with diabetes receiving metformin, not receiving metformin, and patients without diabetes. Outcomes were distant metastasis-free survival (DMFS), recurrence-free survival (RFS), and overall survival (OS). There were 63 patients with diabetes receiving metformin, 67 patients with diabetes not receiving metformin, and 1,318 patients without diabetes. At a median follow-up of 62 months, there were no significant differences in DMFS, RFS, and OS among the 3 groups. Patients with diabetes who did not receive metformin and patients without diabetes had a higher risk of distant metastases, with hazard ratios (HR) of 1.63 (95% CI 0.87 to 3.06) and 1.62 (95% CI 0.97 to 2.71), respectively.

Hadad et al conducted a trial of metformin in women without diabetes receiving neoadjuvant chemotherapy for breast cancer.⁹ The study consisted of a pilot in which all patients were given metformin at 500mg daily for 1 week followed by 1,000mg twice daily for another week leading up to surgery. In a follow up trial, patients were randomized to receive metformin in this regimen or no drug for 2 weeks prior to surgery. The primary

endpoint was expression of Ki67, which is a marker for tumor growth, measured prior to metformin initiation and at time of operation. Ki67 was detected in significantly fewer cells in the metformin group compared to the control for both the pilot and study groups ($p=0.041$ and 0.027 , respectively), suggesting a reduction in tumor growth. Based on these results the authors concluded metformin may have antiproliferative effects in women with breast cancer. This trial was important because it demonstrated the effects of metformin even in patients without diabetes, though it did not measure clinical endpoints.

In conclusion, metformin has been proposed to inhibit tumor growth via a number of mechanisms. In observational studies of patients with diabetes, metformin use has been associated with lower incidence of cancer as well as cancer mortality. In RCTs, however, this finding has not been duplicated. Studies examining metformin as an addition to neoadjuvant chemotherapy in patients with diabetes have had mixed results. In patients with breast cancer without diabetes, metformin use was associated with a secondary marker of tumor growth, though no clinical endpoints were examined. There are numerous studies currently ongoing to further elucidate the role of metformin in various types of cancer, and though it appears to be promising, there is little evidence examining clinical outcomes to support its use currently.⁶

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