

Metformin in Gynecologic Cancers: Opening a New Window for Prevention and Treatment?

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SUMMARY

Metformin is an affordable and well-tolerated drug used in type 2 diabetes. Potential anticancer effects of metformin in gynecologic malignancies include inhibition of the PI3K-mTOR pathway, hormone receptor regulation, and reduction of fibrosis and inflamma-

tion. Multiple studies are currently assessing its role in cancer prevention and as a treatment enhancer.

See related articles by Soliman *et al.*, p. 581, and McCloskey *et al.*, p. 632

In this issue of *Clinical Cancer Research*, McCloskey and colleagues (1) and Soliman and colleagues (2) report preliminary results of the role of metformin on age-related fibrosis of the ovary, and as an enhancer of mTOR inhibitor and hormonal treatment in endometrioid endometrial carcinoma, respectively.

Metformin is an oral biguanide, commonly used as treatment of type 2 diabetes. It was first discovered in 1922, is on the World Health Organization Essential Medicines List, and is the most widely used oral medication for diabetes internationally. Metformin acts in the liver by blocking the mitochondrial redox shuttle and inhibiting gluconeogenesis. A potential protective effect in age associated disorders, including cardiovascular disease, cognitive disorders, and cancer has been described previously (3); in fact, metformin targets multiple cellular pathways of aging, including inflammation, cellular survival, stress defense, autophagy, and protein synthesis (3). Preclinical studies have demonstrated an anticancer effect of metformin via direct and indirect mechanisms of action (Fig. 1). Direct (insulin-independent) effects include activation of adenosine monophosphate kinase (AMPK), leading to inhibition of mTOR, and thus reducing protein synthesis and cell proliferation (3). Contrary to this, indirect (insulin-dependent) anticancer effects include, among others, hepatic AMPK activation, reduction of insulin ligand binding to insulin receptors, and suppression of PI3K, protein kinase B (Akt) pathway, resulting in the inhibition of cell growth and survival. Interestingly, AMPK-mediated suppression of tumor growth factor β production may also prevent organ fibrosis (4). It is possible, both indirect and direct mechanisms of action are relevant in cancer. These preclinical findings provide strong rationale to examine the repurposing of this affordable and well-tolerated agent with over 70-year safety data as prevention and treatment of cancer.

Risk reduction surgery, in women who are germline *BRCA* mutation carriers, is the only validated preventative measure for ovarian cancer. Agents under evaluation include oral contraceptives and the use of

NSAIDs like aspirin to target inflammation (STICs and STONEs, NCT03480776, under investigation in an interventional trial). A Cochrane meta-analysis assessing the role of metformin in endometrial hyperplasia, found insufficient evidence that differences in regression of endometrial hyperplasia or progression to cancer exist between metformin versus metformin in combination with megestrol acetate versus megestrol acetate alone (5). Epidemiologic studies on diabetic patients and meta-analysis have shown a potential role of metformin in prevention of gynecologic malignancies; however, well-designed randomized interventional studies in diabetic and nondiabetic patients are needed, as patient selection and other biases may have been responsible for lower cancer incidence in patients receiving metformin in observational studies (5, 6). A randomized placebo-controlled phase III trial showed low dose metformin was safe and reduced the prevalence and number of colorectal polyps after polypectomy in 1 year in nondiabetic patients (7). A randomized study assessing metformin for endometrial cancer prevention in women with body mass index $> 30 \text{ kg/m}^2$ is currently ongoing (NCT01697566).

Metformin has been assessed as a treatment strategy in combination with chemotherapy and target treatment in multiple disease sites, with often disappointing results (8, 9). A small randomized study showed improved outcomes in progression-free (PFS) and overall survival (OS) when combined with EGFR tyrosine-kinase inhibitors in advanced lung adenocarcinoma (10). Another recent trial showed increased pathologic complete response in patients with HER2⁺ breast cancer receiving standard chemotherapy plus trastuzumab with metformin versus without metformin. This effect was significant in those with the C allele of the *ATM* gene, an allele that has been associated with metformin benefit in diabetics (11). The role of PI3K and mTOR inhibitors in monotherapy has been explored in phase II trials in endometrial cancer showing modest activity (12, 13). As metformin inhibits the PI3K/mTOR pathway and can potentially regulate hormone receptors and decrease estradiol levels (3, 14), metformin combination strategies in certain gynecologic malignancies including low grade ovarian, endometrioid endometrial, and cervical carcinomas are potentially attractive. A randomized phase II study is currently assessing the addition of metformin to carboplatin-paclitaxel in endometrial cancer and ovarian cancer (NCT02122185 and NCT02065687); while, several randomized phase II studies in endometrial cancer are assessing the addition of metformin to hormonal treatment (NCT02990728, NCT03538704, and NCT01686126).

Chronic inflammation is an important hallmark of ovarian carcinogenesis (15). Fibrosis occurs as a result of many chronic inflammatory diseases, and is considered to create a premetastatic niche causing microenvironment changes (4). In this issue McCloskey and

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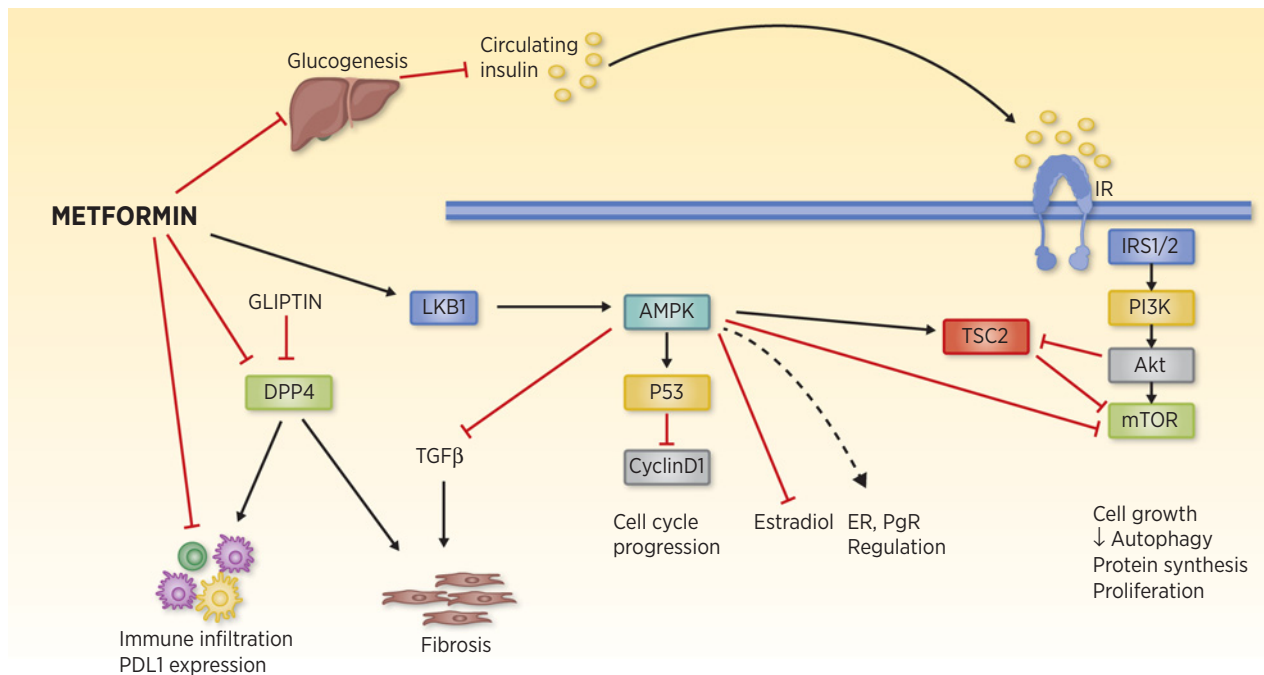


Figure 1.

Preclinical studies have shown potential anticancer effects of metformin. Metformin has possible cancer prevention effects in gynecologic cancers through control of inflammation and fibrosis. Metformin can be potentially used as a treatment enhancer in gynecologic cancers, including (i) cyclin-dependent kinase inhibitors, (ii) hormonal treatment, (iii) PI3K inhibitors, (iv) Akt inhibitors, (v) mTOR inhibitors, (vi) chemotherapy, and (vii) PARP inhibitors. Akt, protein kinase B; DPP4, dipeptidyl peptidase-4; IRS1/2, insulin receptor substrate 1/2; PgR, progesterone receptor; TSC2, tuberous sclerosis complex 2; TGFβ, tumor growth factor β.

colleagues (1) demonstrate age-associated fibrosis in murine ovaries, and they report reduction in fibrosis-related changes in human ovary cohorts with metformin exposure. These findings provide a potential rationale for evaluating the use of metformin for age-associated ovarian cancer prevention. Aged murine ovaries were found to have ovarian fibrosis, which correlated with a distinct microenvironment. These findings were then replicated in a human ovary cohort ($N = 27$; premenopausal 41% and postmenopausal 59%); a significant association between age and human ovarian fibrosis was identified ($P = 0.03$). Human fibrotic ovaries had increased M2 macrophages and $CD8^+$ T-cell infiltration, which was attenuated in metformin-exposed postmenopausal ovaries. While the study presents intriguing results, there are limitations in analysis that will impact future preclinical and clinical investigations. Regrettably, this study excluded ovarian samples from *BRCA* mutation carriers. Two premenopausal women included in the study had evidence of fibrosis and one had a family history of cancer; the authors suggest that other factors beyond age might be related to ovarian fibrosis. Another limitation remains the small number of patients and the fact that tissue was obtained at a single timepoint. Unlike other gynecologic malignancies, obtaining nonmalignant human ovarian tissue from multiple time points to assess the mechanism of action of metformin (preventing fibrosis or restoring the collagen) is not really feasible and alternative approaches such as functional imaging need to be explored. Given the importance of inflammation and fibrosis in ovarian cancer tumorigenesis (15), the role of metformin in prevention of ovarian cancer in high risk women may be worth exploring.

Soliman and colleagues (2) present a phase II study assessing the combination of everolimus 10 mg daily, letrozole 2.5 mg daily, and

metformin 500 mg twice daily, in patients with endometrioid endometrial cancer and ≤ 2 lines of systemic treatment. In an earlier single-arm phase II trial the same group assessed the combination of letrozole and everolimus in patients with non-sarcomatous endometrial cancer histologies and < 2 lines of prior treatment (NCT01068249; ref. 16). Clinical benefit (CB) at 16 weeks was 40%, and objective response rate (ORR) 32%. On subgroup analysis, patients with serous histologies did not benefit from treatment, and ORR in diabetic metformin users was significantly higher than in nonusers. Given these promising results, Soliman and colleagues, designed a phase II trial with triplet therapy where only patients with endometrioid histology were enrolled (7% mixed); prior treatment with metformin and letrozole was permitted. The CB rate was 50% [95% confidence interval (CI), 36.2–63.9], lower than hypothesized by the authors (60%), with an ORR of 28%; while median PFS was 5.7 months (95% CI, 3–8.2) and median OS was 19.6 months (95% CI, 14.2–26.3). Treatment-related adverse events (AE) were mainly grade 1–2 and the most common grade 3–4 AE was anemia (24%), followed by hypertriglyceridemia (15%), and hyperglycemia (9%).

Translational studies were performed to correlate biomarkers with response; a pretreatment biopsy was required and tumor molecular profiling was performed in 47 patients. As expected, the most common alterations were *PTEN* (60%), *PIK3CA* (47%), and *KRAS* (38%). Similar to what has been reported in other studies in endometrial cancer, no differences in outcomes were found based on *PTEN* and *PIK3CA* status, nor in those carrying *KRAS* alterations. Estrogen receptor (ER) was positive in the majority of the patients (91%), while progesterone receptor (PR) was positive in 63%. No differences in CB rate were found based on ER status;

although, a better CB rate was found in PR-positive patients [PR negative 27% (95% CI, 6–61) vs. PR positive 45% (95% CI, 23–68); $P = 0.001$]. In subgroup analysis PR positivity was found to be a potential biomarker of response to treatment, although whether increase in CB rate is derived mainly from the hormonal treatment or the combination remains uncertain.

Soliman and colleagues suggest the triplicate regimen may be synergistic; however, the trial was not designed to address this as it was uncontrolled, and whether benefit was derived from the triple combination, or whether single or two-drug combinations would derive a comparable CB cannot be judged. The CB and ORR rates are comparable with the results of the other phase II studies, including the combination of everolimus and letrozole, led by the same group (16, 17). This study raises many questions and further biomarker focused randomized studies are needed to assess the role of metformin as an enhancer of hormonal and/or PI3K/mTOR inhibitors in endometrial cancer. It is hoped that combination strategies will improve outcome compared with single-agent hormone or mTOR inhibitors in endometrial cancer. The specific combinations used will lead to different toxicity profiles, and incorporation of patient reported

outcome assessment and biomarker discovery for better selection of patients is vital.

Evidence from these two disparate studies sets the foundation for several immediate future investigations. Fibrosis is a hallmark of ovarian cancer, and the potential role of metformin as a prevention strategy is intriguing; a more detailed study evaluating ovaries from high risk women is warranted. Hormonal treatment remains one of the main treatment strategies in endometrial cancer, but ORRs are low and single-agent studies with mTOR inhibitors in endometrial cancer have also had modest results. The promise of combinations needs to be evaluated objectively with rationally designed controls, which would provide much needed context for any improvement in outcome, as well as increase in toxicity.

Disclosure of Potential Conflicts of Interest

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