

Impact of Metformin on Advanced Pancreatic Cancer Survival: Too Little, Too Late?

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Metformin offers no survival advantage in patients with metastatic pancreatic cancer. Despite promising experimental evidence suggesting an antitumor effect of metformin, its impact on the survival of advanced pancreatic cancer is likely

very limited. Future studies may need to consider its role in early-stage pancreatic cancer. *Clin Cancer Res*; 22(5); 1031–3. ©2015 AACR.

See related article by Reni et al., p. 1076

In this issue of *Clinical Cancer Research*, Reni and colleagues report the results from an open-label, randomized, phase II trial investigating the effect of metformin in patients with metastatic pancreatic cancer (1). Study patients were randomized to receive a chemotherapeutic regimen [i.e., cisplatin, epirubicin, capecitabine, and gemcitabine (PEXG)] with or without metformin at a dose of 2 gm daily. On the basis of a preplanned interim analysis performed after the first 60 patients were enrolled, metformin use was not associated with a survival benefit, and the trial was terminated early for futility. Overall survival at 6 months was 52% [95% confidence interval (CI), 33–69] in the control group and 42% (95% CI, 42–59) in the metformin group; $P = 0.61$.

Pancreatic cancer is a leading cause of cancer-related death in the United States and projected to be the second leading cause of cancer-related death by 2020 (2). Despite new chemotherapeutic agents, improved surgical technique, and growing experience in the last two decades, the mortality rate has remained unchanged. Patients with local disease at diagnosis are potential candidates for surgical resection, but the vast majority of the patients with pancreatic cancer present with unresectable metastatic disease. Treatment for locally advanced and metastatic pancreatic cancer involves chemotherapy and is generally palliative in nature. There are two predominantly used initial chemotherapeutic regimens: (i) gemcitabine in combination with nab-paclitaxel (3) and (ii) combination chemotherapy known as FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; ref. 4). Both regimens have been shown to offer only modest mortality benefit. More recently, immunotherapy offers potential promise (5).

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doi: 10.1158/1078-0432.CCR-15-2494

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Metformin is a biguanide used as an oral hypoglycemic agent in the treatment of type 2 diabetes mellitus. The mechanism of action by which metformin lowers blood glucose is not entirely understood, but it appears to involve decreasing hepatic glucose production and increasing insulin sensitivity. Metformin is inexpensive and well tolerated, thus making it a suitable candidate as a chemopreventive agent. It has been evaluated as a therapeutic agent in nondiabetic conditions such as polycystic ovary syndrome and nonalcoholic steatohepatitis (6, 7). *In vitro* studies suggest that metformin may inhibit the growth of pancreatic cells through several mechanisms (Fig. 1). One mechanism is related to its effects on lowering insulin and insulin-like growth factor 1 levels. Metformin may also have direct inhibitory effects by activating the AMPK protein, a serine/threonine kinase activated in adenosine monophosphate-rich states and hypoxia (8). AMPK, in turn, phosphorylates and inactivates proteins in the mTOR pathway, a regulatory pathway that inhibits cell proliferation, polarity, and division (9).

Consistent with these experimental data, metformin has been found in some observational studies to be associated with reductions in the incidence of and mortality from various cancers including pancreatic cancer (10, 11). However, the validity of many of these studies has been questioned because time-related biases (e.g., immortal-time bias) could have led to the observed benefit (12). Furthermore, two (13, 14) of the three studies that specifically examined the impact of metformin on pancreatic cancer survival failed to observe a survival benefit from metformin in pancreatic cancer patients, particularly among those with advanced disease. Therefore, observational data were inconclusive with regard to a clinically apparent beneficial effect of metformin on pancreatic cancer risk and outcome.

The trial by Reni and colleagues (1) from Italy along with another recent multicenter, double-blind, randomized, placebo-controlled phase II trial from the Netherlands (15) provide much needed clarity on this issue. Despite many differences in study design between the two trials (e.g., eligible cancer stage, chemotherapy regimen, blinding, use of placebo, and interim analysis/early termination), their results are remarkably consistent. They both demonstrate that metformin at a dose typical for glycemic control is unlikely to impart a survival benefit in patients with metastatic pancreatic cancer.

There is no shortage of examples where compelling experimental evidence of a drug effect, either beneficial or harmful, fails to

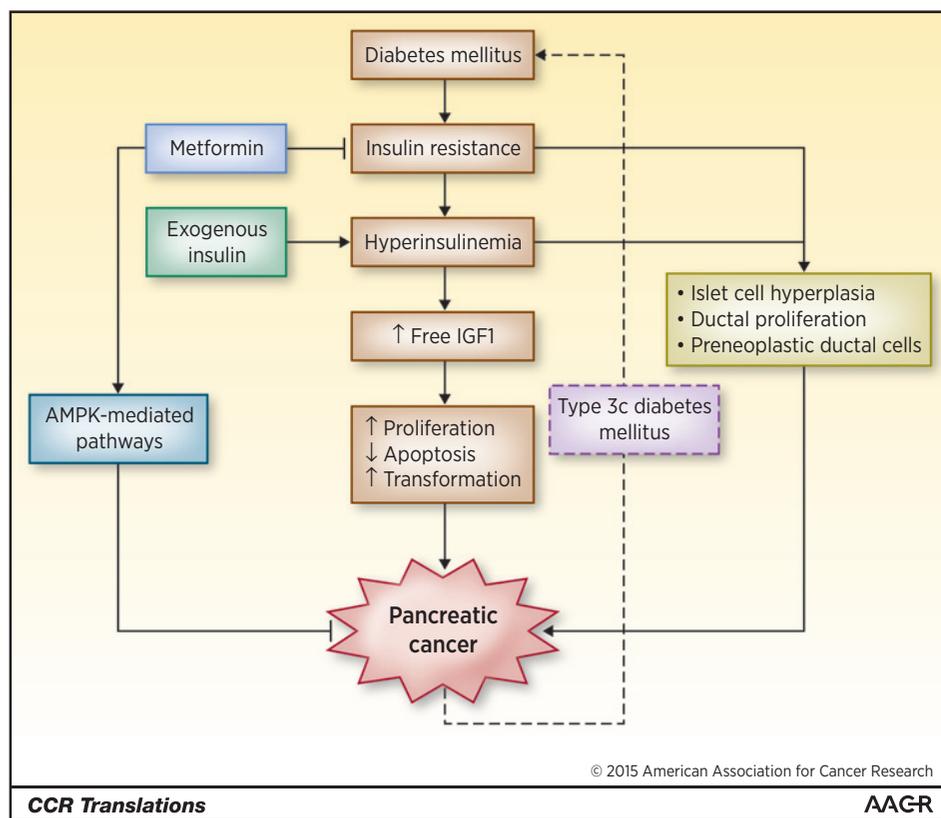


Figure 1. Proposed mechanisms linking diabetes, metformin, and pancreatic cancer.

translate into a clinically important difference (e.g., statin as a chemopreventive agent for colorectal cancer). One possible reason is that the drug concentration in the target tissue necessary to observe an effect on the bench side might not be attainable with the drug doses typical for its usual clinical indication(s). Another explanation for the lack of survival benefit might be that the antitumor effect of metformin is too modest to be clinically important in the setting of large tumor burden and aggressive tumor biology. Indeed, none of the previous observational studies demonstrated a survival benefit of metformin in patients with advanced stage pancreatic cancer (11, 13, 14).

In conclusion, the study by Reni and colleagues (1) contributes important data on a controversial issue. It corroborates the findings from another clinical trial. These clinical trial data can help guide the focus of future studies in this line of research. For example, they support the rationale for the ongoing exploration on the potential role of metformin as a form of maintenance therapy in patients with stabilized metastatic cancer (ClinicalTrials.gov: NCT02048384) or perhaps metformin might be worth

evaluation in the neoadjuvant setting. They also point to the need for clinical trials to determine whether metformin offers any survival advantage among patients with resectable pancreatic cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Writing, review, and/or revision of the manuscript: Y.-X. Yang, A.K. Rustgi
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y.-X. Yang

Grant Support

This work was supported by the NIH under award numbers P30DK050306 (to Y.-X. Yang and A.K. Rustgi) and R01DK060694 (to A.K. Rustgi).

Received November 3, 2015; revised November 7, 2015; accepted November 13, 2015; published OnlineFirst December 4, 2015.

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Clinical Cancer Research

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Clin Cancer Res 2016;22:1031-1033. Published OnlineFirst December 4, 2015.

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