ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Metformin's Potential in Oncology

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H&O Please provide an overview of metformin. What is known about its mechanism(s) of action?

MP Metformin is an oral biguanide commonly used in the management of type 2 diabetes mellitus. Guanidine is a natural substance found in certain plants, and biguanides are based on this chemical structure. Although the precise mechanism of metformin's antineoplastic activity is not well defined, it has been proposed to involve activation of the liver kinase-B1 (LKB1) and AMP-activated protein kinase (AMPK) pathway. Metformin inhibits mitochondrial respiratory chain complex I, which leads to decreased intracellular ATP and an increase in the ratio of intracellular AMP to ATP. Owing to this change in the energy status of the cell, the LKB1/AMPK pathway is activated, in turn phosphorylating TSC2, which results in inhibition of mTORC1 signaling and downregulation of energy-consuming processes in an attempt to maintain cellular energy homeostasis. Through its activity on hepatocytes, metformin may indirectly inhibit tumor cell proliferation. This results in decreased hepatic glucose secretion and ultimately decreased serum insulin, a known mitogen for a subset of cancer cells.

H&O What led to the current interest in the use of metformin for cancer prevention and treatment?

MP The potential for application of metformin in oncology was first recognized in retrospective epidemiologic studies of diabetic patients with cancer. A number of observational studies reported decreased cancer incidence and cancer-related mortality in patients with diabetes who were receiving standard doses of metformin (1500 to 2250 mg/day in adults). In 2005, a report in the *BMJ* by Evans and colleagues demonstrated a reduced risk of subsequent cancer diagnosis in diabetics who were receiving metformin vs those patients not receiving the drug; the protective effect increased with greater metformin exposure. Other studies involving multiple forms of cancer have reported reduced cancer risk in diabetics receiving treatment with metformin vs no metformin treatment, as well as lower cancer-related mortality in patients receiving metformin compared with those receiving other standard diabetic therapies. However, in other studies of diabetic cancer patients, metformin use was not associated with benefit. Thus, the need for additional clinical research is crucial in order to fully appreciate the impact of metformin on cancer recurrence and survival.

H&O What are areas of concern regarding retrospective studies of diabetic patients treated with metformin?

MP Dozens of retrospective studies claim to show that diabetic patients who receive metformin have a lower risk of cancer or better cancer prognosis than patients with diabetes who do not receive metformin. These studies, however, are controversial and lacking in definitive proof. Rather, they are best regarded as hypothesis-generating

studies. In a critique published in 2013 in *Diabetes Care*, Suissa and associates highlighted important methodologic concerns with many of these studies, namely time-related bias and the statistical methods used.

H&O What have laboratory models demonstrated?

MP Laboratory models were undertaken to follow up on the pharmacoepidemiologic clues of metformin. Perhaps surprisingly to some observers, these models have consistently demonstrated metformin's antineoplastic activity. However, the overarching issue with these models is that many use concentrations of metformin that are considerably higher than those used in diabetes treatment.

H&O Why else should these clues be interpreted with caution?

MP There are very exciting clues from laboratory studies and population studies that metformin may improve cancer outcomes or lower cancer risk. However, it is crucial to conduct more laboratory and clinical studies in order to find the optimal dose, to understand in what disease situations the drug may be most beneficial, and to determine if metformin itself or a metformin derivative would be most suitable for trials.

H&O How can future clinical trials of metformin be improved?

MP Clearly, further studies are necessary to clarify the role of this agent in cancer prevention and therapy. Moving forward, research should aim to identify key patient and tumor factors that govern metformin sensitivity, which is critical for the design of clinical trials and the identification of patients best suited for metformin treatment. Given that metformin has a favorable toxicity profile, is relatively inexpensive, and has shown antiproliferative activity both in vitro and in vivo in preclinical studies, researchers should be encouraged to carry out additional clinical trials on this agent. Unlike newly synthesized drug candidates, the use of metformin is not controlled by a pharmaceutical company with intellectual property rights. This is one of the reasons why there are more than 100 trials of metformin ongoing in oncology. However, not all of these are well designed or carefully controlled. It is essential that ongoing and future studies include strong embedded correlative research components, with evaluation of host and tumor factors to identify potential predictors of metformin benefit and, more importantly, to allow for an enhanced understanding of the relative contributions of indirect insulin-mediated and direct insulin-dependent metformin action. The absence of pharmaceutical industry interest in metformin has led to less coordination of research activities than what is commonly seen in anticancer drug development. Consequently, it is essential for the research community to ensure that this function is fulfilled and that a major focus on clinical translation and relevance emerges in future research.

H&O What do you think the future holds?

MP The clues regarding metformin and other biguanides are tantalizing, but some of the ongoing trials are based on incomplete data regarding dosing, therapeutic combinations, and predictors of efficacy. Almost all clinical trials are testing conventional doses used in patients with diabetes, which may not be optimal for applications in oncology. The first generation of clinical trials may be followed by a second generation of trials that consider these issues. Trials of novel biguanides also may be expected in the future, if the private sector invests in drug development in the area. Currently, there are a number of clinical trials evaluating the use of metformin as a cancer therapy, including studies in prostate, breast, colorectal, endometrial, and pancreatic cancer. Together with new pathophysiologic investigations, these studies should help to further elucidate the role of metformin as an anticancer agent.

Suggested Readings

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