

Metformin as an Anticancer Drug: A Commentary on the Potential Therapeutic Strategy and Underlying Mechanism of Metformin in Gastric Cancer

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Commentary

Metformin therapy is a burst of interest in cancer chemoprevention and therapeutic strategies [1-4]. Epidemiological studies based on cohorts with type 2 diabetes revealed that metformin usage was associated with a reduced risk for various cancer, including breast, colorectal, prostate and pancreas cancers [5]. Meanwhile, the efficacy of cancer chemopreventive effect of metformin has achieved positive results in multiple target organs, especially, colon and mammary cancer [6]. However, only few epidemiological evidences supported the positive link between type2 diabetes and an increased risk of gastric malignancies [5].

In the past several years, however, increasing evidences displayed a promising and attractive prospect of the usage of metformin in gastric cancer (GC). Kim YI et al. gave the first evidence that long term use of metformin (>3 years) in type 2 diabetics is associated with a significantly reduced gastric cancer risk, especially for those who do not use insulin [7]. The following studies confirmed that cumulative duration of metformin use could decrease cancer-specific mortality rates and improve survival among GC patients with diabetes who underwent gastrectomy in three cohorts [8-10]. Meanwhile, Yu G et al. systemically detected the effect of metformin on multiple GC cells in vitro and in vivo and confirmed the anti-cancer effects of metformin in GC [9]. All these data support metformin as a potential anticancer treatment in GC patients. However, therapeutic options and the cumulative doses of metformin remain to be explored. Firstly, clinical experiments have identified metformin as an adjuvant drug combined with chemotherapeutic drugs to improve treatment efficacy [11]. Yu G et al. also proved that metformin alone could not completely inhibit tumor growth in mice, but it could sharply enhance cisplatin- or rapamycin-induced reduction of tumor growth [9]. Therefore, it suggested that metformin could be a valuable additional therapy in cancer patients treated with conventional chemotherapy.

The next question is to choose the appropriate doses and the right time. High doses of metformin might lead to drug-resistance [9]. A dose less than commonly used in clinical practice is also proposed [6]. Therefore, trials on the effect of metformin at various doses levels will be necessary to explore the most optimal regimens for GC. Kordes S et al. revealed that metformin offers no survival advantage in patients with metastatic pancreatic cancer [12]. Considering the poor status and relatively shorter survival of these patients, we believe that metformin administration should be performed in early-stage cancer patients.

The third question is the duration of the usage of metformin as an anticancer drug. Several short-term intervention studies of metformin on breast cancer were summarized and the results were inconsistent [2]. Kim YI et al. reported that three years usage of metformin is

associated with reduced risk of gastric cancer [7]. Yu G et al. treated GC cancer cells with metformin and revealed that metformin treatment firstly activated PTEN and CDKN1, inhibiting cell proliferation, and then decreased the expression of genes involved in tumor invasion [9], supporting long term of metformin usage as a potential anticancer strategy. However, long term use of metformin has been found to be associated with increased risk of vitamin B12 deficiency [13]. Therefore, the concentration of vitamin B12 should be monitored and vitamin B12 should be complemented if necessary. These data suggest that studies on metformin administration should design the different duration times of the metformin usage.

Metformin inhibits tumor cell growth through activating LKB1/AMPK pathway and the immune system, inducing cell cycle arrest and/or apoptosis, and damaging mitochondria respiratory chain (oxidative phosphorylation system). Besides these AMPK-dependent mechanism, Yu and his colleagues revealed novel AMPK-independent pathways of metformin inhibiting tumor cell growth, including activating PTEN and inactivating MMP7 and DCN [9]. Moreover, microarray analysis revealed numerous potential targets of metformin, which needs to be investigated in the future.

In summary, all present data supported the important role of metformin as an antineoplastic agent in GC. However, a large, double-blind, randomized, placebo-controlled clinical trial will be necessary to support or reject the therapeutic value of metformin in GC.

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References

1. Sui X, Xu Y, Wang X, Han W, Pan H, et al. (2015) Metformin: A Novel but Controversial Drug in Cancer Prevention and Treatment. *Mol Pharm* 12: 3783-3791.
2. Grossmann ME, Yang DQ, Guo Z, Potter DA, Cleary MP (2015) Metformin Treatment for the Prevention and/or Treatment of Breast/Mammary Tumorigenesis. *Curr Pharmacol Rep* 1: 312-323.
3. Anisimov VN (2016) Metformin for Prevention and Treatment of Colon Cancer: A Reappraisal of Experimental and Clinical Data. *Curr Drug Targets* 17: 439-446.
4. Chan AT (2016) Metformin for cancer prevention: a reason for optimism. *Lancet Oncol* .
5. Nicolucci A (2010) Epidemiological aspects of neoplasms in diabetes. *Acta Diabetol* 47: 87-95.
6. Anisimov VN (2015) Metformin for cancer and aging prevention: is it a time to make the long story short? *Oncotarget* 6: 39398-39407.

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7. Kim YI, Kim SY, Cho SJ, Park JH, Choi IJ, et al. (2014) Long-term metformin use reduces gastric cancer risk in type 2 diabetics without insulin treatment: a nationwide cohort study. *Aliment Pharmacol Ther* 39: 854-863.
 8. Lee CK, Jung M, Jung I, Heo SJ, Jeong YH, et al. (2016) Cumulative Metformin Use and Its Impact on Survival in Gastric Cancer Patients After Gastrectomy. *Ann Surg* 263: 96-102.
 9. Yu G, Fang W, Xia T, Chen Y, Gao Y, et al. (2015) Metformin potentiates rapamycin and cisplatin in gastric cancer in mice. *Oncotarget* 6: 12748-12762.
 10. Greenhill C (2015) Gastric cancer. Metformin improves survival and recurrence rate in patients with diabetes and gastric cancer. *Nature reviews Gastroenterology & hepatology* 12: 124.
 11. Zhang HH, Guo XL (2016) Combinational strategies of metformin and chemotherapy in cancers. *Cancer Chemother Pharmacol* .
 12. Kordes S, Pollak MN, Zwinderman AH, Mathot RA, Weterman MJ, et al. (2015) Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol* 16: 839-847.
 13. Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, et al. (2016) Long-term Metformin Use and Vitamin B12 Deficiency in the Diabetes Prevention Program Outcomes Study. *J Clin Endocrinol Metab* 101: 1754-1761.