



# Administration of metformin to increase the efficacy of chemotherapy regimen in cancers; a new look to an old drug

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## Abstract

Chemotherapeutic agents are still the major and most common therapy to prevent tumor growth. These drugs have various adverse effects in different organs in addition to systemic effects. Finding more specific and effective drugs or new adjuvant therapeutic substance is needed to improve the success rate. Several studies have proposed the possible mechanisms of anti-neoplastic of metformin, however, its exact mechanism is still obscure. The suggested mechanisms are; alteration in the host metabolic environment after administration of metformin, such as decreases in insulin-dependent stimulation of tumor growth or direct effect on cancer cells, such as the impact on adenosine monophosphate (AMP)-activated protein kinase signaling pathway. Metformin, as an adjuvant therapy, synergistically exerts growth inhibitory effects against cell growth and can induce cell apoptosis in an animal model. Adding metformin to the chemotherapy regimen may reduce resistance and enhance therapeutic efficacy.

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## Introduction

Malignancy is still one of the most challenging illnesses to treat despite much progress in recent years. Mortality rate has been reduced only marginally due to the intrinsic behavior of tumors, heterogeneous nature of malignancy and different degrees of response to treatment (1,2).

Cancer cells are recognized and defined by their high production rate and resistance to apoptotic cell death. Chemotherapeutic agents are still the major and most common therapy to prevent tumor growth. The side effects of chemotherapy agents have negative impacts on the quality of life. Meanwhile, malignant cells frequently became resistant to chemotherapy, which results in cancer reappearance or metastasis. Chemotherapeutic agents express antitumor properties by preventing cancer cell growth through cell cycle arrest and stimulation of cellular apoptosis. Progression to advance stages or metastasis is a common

## Key point

Numerous epidemiologic studies show the ameliorating impact of administration of metformin to chemotherapy regimens on the remission of cancers.

scenario in the current chemotherapy era. Chemotherapeutic drugs have various adverse effects in different organs in addition to systemic effects. Common systemic adverse effects include loss of appetite, fatigue, infertility, nausea, vomiting, and hair loss. These side effects may lessen with reducing the dosage of chemotherapeutic agents. However, it may diminish the effectiveness of chemotherapeutic drugs to inhibit tumor growth. Therefore, finding more specific and effective drugs or new adjuvant therapeutic substance is needed to improve the success rate (3,4). Mammalian cell death occurs by various mechanisms, including apoptosis, necrosis and



autophagy. Autophagy is a catabolic activity which leads to modification of cytoplasmic materials. This process leads to organelle impairment and accumulation of abnormal proteins. Autophagy is activated by different mechanisms and occurs in various malignant cells. Metformin, activates the autophagy pathway and hence, might be a candidate to use as an adjuvant therapy in cancer treatment (5, 6).

### Materials and Methods

Web of Science, directory of open access journals (DOAJ), PubMed/Medline, EBSCO, Embase, Scopus, and Google Scholar were searched using keywords of chemotherapy, metformin, cancer, tumor, type 2 diabetes, adjuvant therapy, malignancy and adenosine monophosphate (AMP)-activated protein kinase

### Metformin in type 2 diabetes

Metformin is the first line of antidiabetic agent for diabetes mellitus type II. Metformin is a relatively cheap and well tolerated drug. It has a low risk of hypoglycemia and advantage of countering insulin resistance. Approximately 120 million prescriptions are filled globally each year because of its positive risk-benefit profile (7).

### The pathophysiology of antitumor effects of metformin

Several studies have proposed the possible mechanisms of anti-neoplastic of metformin. However, its exact mechanism is still obscure. The suggested mechanisms are alterations in the host metabolic environment after administration of metformin, such as decreases in insulin-dependent stimulation of tumor growth. Metformin may also have a direct effect on cancer cells. Metformin reduces insulin/insulin-like growth factor 1 (IGF-1), insulin receptor and/or IGF-1 receptors. In diabetes, increasing insulin and IGF-1 receptor or hyperglycemia, have been perceived to provoke mitosis and tumor growth. Metformin opposes these signaling routes and potentially might be beneficial in reducing multidrug resistant cancer and prevention of tumor metastasis (8, 9).

Metformin also inhibits the glycolysis and perturbation of electron transport chain in the tricarboxylic acid cycle. This phenomenon decreases ATP creation and depletion of cellular aspartate, which is vital for nucleotide synthesis. This pathway may explain the anticancer activity of metformin (10, 11).

Metformin increases the level of AMP and prevents adenylate cyclase activity and mTORC1 signaling. Metformin causes a temporary reduction in cellular energy status, which causes a total decrease in ATP using processes. In proliferating cells like malignancies, this phenomenon may stimulate a cytostatic condition which will reduce the proliferation of cells. In fact, malignant cells in the presence of metformin cannot balance the reduced energy condition, thus cells will go toward apoptosis (12-14).

### Adenosine monophosphate -activated protein kinase (AMPK)

AMP-activated protein kinase is a heterotrimeric complex designed by three subunits; alpha, beta and gamma. The alpha subunit is accountable for the catalytic action while the beta and gamma subunits are related to the changes of the kinase activity.

To stimulate its kinase activity, AMP-activated protein kinase should be phosphorylated on the residual alpha subunit by liver kinase B1 (LKB1). This phosphorylation is delicately moderated by allosteric modifications. Numerous studies have shown that administration of metformin results in a decrease in ATP in hepatic cells and a reduction in the ATP/ADP ratio, leading to a drop in cellular bioenergetics.

Metformin also causes stimulation of intracellular hepatic enzyme of AMP-activated protein kinase which leads to an increase in beta-oxidation, or autophagy. This pathway is required for the regulation of cell proliferation and energy metabolism.

AMP-activated protein kinase is an important moderator of various processes within the cells. The dysregulation of AMPK accompanies numerous pathological situations, such as diabetes, neurodegeneration, malignancy, and heart disease. In fact, when AMPK is triggered, incipient malignant cell death may happen in the absence of sufficient energy stores. Various conditions can stimulate AMPK in the body, such as calorie restriction, which depresses cellular energy supplies and triggers AMPK. This is the reason that calorie constraint has been detected to diminish malignancy occurrence and augment cancer cell death in animal models (15-18).

Metformin also hinders mitochondrial complex I activation in various malignant cells, which consequently reduces tumorigenesis. In addition, metformin provokes cells to preserve or reduce energy or may halt abnormal cell growth completely.

Metformin enhances the effectiveness of cytotoxic T cell via programmed death-ligand 1 (PD-L1) on cancer cells. The mechanism by which metformin enhances the cytotoxicity of cancer drugs is dependent on the presentation of the energy sensor kinase AMPK in malignant cells.

Metformin activates AMPK, which phosphorylates synthesized PD-L1 in the endoplasmic reticulum lumen. This phosphorylation results in abnormal N-glycosylation of PD-L1 and prevents its development within the Golgi apparatus and degradation in endoplasmic reticulum. Therefore, metformin causes malignant cells to be more susceptible to cytotoxic T cells (19-22).

### Metformin and mitochondria

Metformin attracts and aggregates in mitochondria because of its positive molecular charge. Subsequently, it prevents the complex I of the mitochondrial electron transport

chain, leading to a decline in cellular ATP and a rise in both AMP/ATP and ADP/ATP ratios. Low energy level activates AMPK, a key energy sensor, which is implicated in various activities within the cells to reestablish energy homeostasis (23-25).

Activation of AMPK directs the cells toward an anti-proliferative capability that leads to inhibition of tumor expansion. (26-28). Moreover, metformin impedes the mitochondrial glycerophosphate dehydrogenase (29-31).

## Discussion

Iliopoulos et al showed that metformin prevents the growth of breast cancer cells in animal models. It has been observed that the co-administration of metformin and doxorubicin enhances the proportion of cancer regression and delay of relapse, in comparison to treatment with doxorubicin alone (32). Another retrospective study demonstrated a higher frequency of complete remission of breast cancer in diabetic patients on metformin compared to diabetic individuals taking other anti-diabetic agents while undergoing chemotherapy (33). Xu et al demonstrated that metformin inactivates stromal fibroblasts in ovarian cancer and reduced fibroblast-facilitated tumor growth in their models. They concluded that metformin prevents interleukin 6 secretion through inhibiting NF- $\kappa$ B signaling, the upstream controller of stromal inflammation. It is postulated that an alternative modality in targeting stromal inflammation by a potential plan of combination therapy with metformin may ameliorate the chemo-sensitivity in ovarian cancer (34). A meta-analysis/systematic review by Coyle et al, suggested that metformin could be a suitable adjuvant therapy in prostate and colorectal malignancies, especially in individuals who received radical radiotherapy (35). Xin et al conducted a study on MCF-7 breast cancer cells. They demonstrate that the combination of formononetin and metformin potentiate cell growth inhibition, and the initiation of apoptosis in MCF-7 cells mediated by the ERK1/2 signaling pathway (36). Jafari-Gharabaghlu et al have also demonstrated the anti-proliferative properties of metformin and phenformin in combinational therapy, against breast cancer cells. In their experiment, the combination of metformin and phenformin enhanced the efficacy of treatment (37). Hamed et al conducted a randomized clinical trial on individuals with primary ovarian cancer with a 4-year follow-up period. They divided their patients into two study groups. The study arm received 500 mg metformin three times a day in addition to a standard chemotherapy regimen while the control arm received only the standard chemotherapeutic drugs after surgery.

This study demonstrated that the addition of metformin to the chemotherapy regimen of patients undergoing surgery for ovarian cancer can improve the survival (48 months vs. 25.7 months in the control group) and declining the rate of relapse (13.3% vs. 67.5% in the control group).

It is possible that metformin intensifies the cytotoxic effects of chemotherapy in tumor cells and other tissues by modifying various gene presentation routes (38). In a recent multicenter randomized phase II trial, Narita et al compared the efficacy and safety of chemotherapy regimens by adding metformin in patients with resected pancreatic ductal adenocarcinoma. Metformin is administered in conjunction with chemotherapy for two years. It has been shown that 2-year-survival rate improved from 65% in the control group to 78% in the study group. It also demonstrated an improvement of the 5-year survival rate to 44.1%. This epidemiologic study suggests that metformin may have a favorable impact on the prognosis of pancreatic ductal adenocarcinoma (39). Kuo et al conducted a study on head and neck squamous cell carcinoma. They compared the combination of metformin to cisplatin treatment versus cisplatin alone. They measured cell proliferation level by MTS assays. This observation demonstrated that metformin protects head and neck squamous cell cancer against cisplatin in vitro (40). Sharma et al demonstrated that metformin notably diminished cholesterol content in breast cancer cells with parallel inhibition of several cholesterol regulatory genes. The authors concluded that anticancer activity through decreasing cholesterol content in breast cancer cells is one of the anticancer mechanisms of metformin (41). Chen et al observed that proliferation of gastric cancer cells is reduced by exposure to metformin. The suppressive impact of metformin on gastric cancer is mediated through stimulating calmodulin-like protein 3 secretion from tumor-associated fibroblasts (42).

Mitochondrial glycerol 3-phosphate dehydrogenase is a main provider of electrons to the transport chain in mitochondria. This enzyme is necessary for gluconeogenesis. Mitochondrial glycerol 3-phosphate dehydrogenase is also the main enzyme linking oxidative phosphorylation and glycolysis. This enzyme is a target of metformin in the liver. Thakur et al have demonstrated that mitochondrial glycerol 3-phosphate dehydrogenase is overexpressed in thyroid cancer. Metformin decreases this enzyme expression, inhibits mitochondrial respiration and stops the shift of cancer cell metabolism toward glycolysis (43).

## Conclusion

Administration of metformin as an adjuvant therapy synergistically exerts growth inhibitory effects against cell growth and can induce cell apoptosis. Adding metformin to the chemotherapy regimen may reduce resistance and enhance therapeutic efficacy.

## Authors' contribution

NH, BG, NN, PN and BY wrote the paper. RT edited the manuscript. All authors read and signed the final paper.

## Conflicts of interest

The authors declare no conflict of interest.

**Ethical considerations**

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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