Chapter

Metformin and Its Implication in Cancer Therapy

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Abstract

Metformin has been used for almost half a century as the first line of treatment for type 2 diabetes. Mechanisms of action are still incompletely known, recent studies have shown that metformin exerts its effects through several mechanisms, including the stimulation of AMP-activated protein kinase, decreasing production of cyclic AMP, inhibition of mitochondrial complex I of the electron transport chain, targeting glycerophosphate dehydrogenase and altering gut microbiota. In recent years, studies have shown that patients with type 2 diabetes mellitus have a lower risk of developing cancer, and patients with cancer and type 2 diabetes have a lower mortality. Experimental studies have demonstrated that metformin has anti-tumor activity by inhibiting mTORC1 signaling pathway and mitochondrial complex, inhibiting tumor growth and proliferation, and inducing cellular apoptosis. There are multiple studies showing that combination of metformin with different types of anti-cancer therapies may reduce toxicities and tumor resistance. This chapter is focused on the progress made in understanding the anti-tumor effect of metformin and its association with cancer therapy.

Keywords: metformin, cancer, chemotherapy, targeted therapy

1. Introduction

Guanidine derivatives, metformin, buformin and phenoformin, were discovered in the 1920s, extracted from the isoamylene plant [1]. Metformin it is a biguanide extracted from herb *Galega officinalis*, and it was first proposed by Emile Werner and James Bell in 1922, when they found that metformin is reducing the amount of glucose in rabbits and does not affect heart and blood pressure [2, 3]. Due to the increased risk of lactic acidosis and of cardiac death, buformin and phenoformin were withdrawn from the market in 1970 [4]. Due to the good safety profile of metformin, the use of this drug was extended beyond type 2 diabetes to ovarian polycystic disease, gestational diabetes, diabetic nephropathy and cardiovascular complications associated with type 2 diabetes [5].

The association between cancer and diabetes was first proven in 1930 by Marble [6]. Over the past 20 years, numerous studies have shown that diabetic patients have a higher incidence of cancers, increased mortality [7, 8], and the fact that patients with diabetes and cancer are less sensitive to chemotherapy [9–11].

Regarding the anti-tumor effect of metformin, numerous studies have shown that metformin-treated diabetes patients have a low incidence of cancers and low mortality compared with patients treated with other types of anti-diabetics such as sulfonylureas or insulin [9, 12, 13].

In vivo and in vitro studies have demonstrated that metformin has an anti-tumoral effect both directly and indirectly, which translates into inhibition of tumor cell proliferation, induction of apoptosis, and cell cycle arrest [14–16].

Taking all these into consideration, metformin appears to be useful as an adjuvant to cancer treatment.

2. Anti-tumor mechanism of action of metformin

Metformin's mechanisms of action and its anti-tumor effects are multiple and have been described over the years in numerous studies, both in vivo and in vitro, but they are not yet completely understood. The main mechanisms of actions are activation of liver kinase B1 (LKB1) and AMP-activated kinase (AMPK), and inhibition of mammalian target of rapamycin (mTOR). Other mechanisms described in literature are inhibition of protein synthesis, activation of apoptosis by p21 and p53, inhibition of unfolded protein response (UPR), activation of immune system, prevention of angiogenesis, reduction of blood insulin levels and reduction of hyperlipidemia [17, 18].

Metformin is entering the cells with the help of organic cation transporter 1 and 3, and as a result is blocking the complex I of electron transfer chain (ETC) and an enzyme named mitochondrial glycerophosphate 3 dehydrogenase (mGDP). Introduction of Metformin into the cell results in reduced activity of adenosine triphosphate (ATP) and reduced oxygen consumption, which further increase the levels of adenosine monophosphate within the cells and activate AMPK, and in the end this will put the cells under stressful conditions [19, 20].

Metformin inhibits mTOR pathway by activating LKB1 and AMPK, resulting in reduction of protein synthesis and inhibition of angiogenesis. AKPK inhibits mTOR pathway by activation of tuberculous sclerosis complex (TSC2) and by direct phosphorylation of co-signaling molecules that will attached to mTOR molecules [21, 22]. Metformin is also inhibiting mTOR by reducing phosphorylation of ribosomal protein S6 kinase (S6Ks) [23].

Ataxia teleangectasia mutated (ATM) and LKB1 are proteins with an important role in cell cycle. Both ATM and LKB1 are tumor suppressors. The response of ATM to metformin is phosphorylation of LKB and in the end the activation of AMPK [24].

Inhibition of unfolded protein response (UPR) is another mechanism by which metformin exerts its anti-tumor effect. UPR activity is vital for cell survival of under stress conditions. Metformin inhibits the activity of UPR and determine cells to undergo apoptosis [25].

Insulin and insulin growth-like factor (IGF) promote mitosis and cell growth and inhibit apoptosis. All this processes are very important in carcinogenesis and the relation between hyperinsulinemia, insulin resistance and cancer promotion are well known [26]. Metformin inactivates I/IGF pathway by reducing blood insulin levels and by inhibiting glucose absorption by intestinal cells [27, 28].

3. Metformin: epidemiologic evidence of its anti-tumor effect

Metformin was approved by Food and Drug Administration (FDA) in 1957 for type 2 diabetes and became the first line treatment due to its superior safety profile and hypoglycemic and cardiovascular protective effect [29].

The effect of metformin on cancer risk reduction was first observed in a study published in 2005 by Evans et al., which included 11,776 patients with type 2 diabetes; this observation was reiterated in another trial in 2009, involving more than 4,000 patients with diabetes treated with metformin, the risk of developing cancer being 7.3% for patients receiving metformin vs. 11.6% in the control group [30, 31].

In 2009, a study conducted at the MD Anderson Cancer Center by Li et al., showed that metformin use is associated with a low risk of pancreatic cancer in patients with type 2 diabetes [32].

A very large retrospective study that evaluated more than 62.000 patients with diabetes showed that metformin treatment reduces the risk of cancer compared to other antidiabetic therapies (insulin, sulfonylureas), and also showed that the combination of metformin with insulin or sulfonylureas reduces the risk of cancer associated with these therapies. This study showed that the risk of developing colorectal and pancreatic cancer is higher in patients with diabetes treated with insulin, compared to patients treated with metformin, and that metformin does not reduce the risk of breast or prostate cancer [33].

In terms of mortality, in 2006 a study conducted by Bowker el al, retrospectively reported that mortality is higher in patients with type 2 diabetes using insulin and sulfonylurea, comparing with those using metformin [34].

In 2010, a prospective study, ZODIAC-16, evaluating the influence of metformin on cancer mortality in 1353 patients with type 2 diabetes showed that metformin-treated patients had a lower mortality rate (with a median of 9.6 years) compared to the control group [35].

3.1 Metformin in hepatocellular carcinoma and pancreatic cancer

Hepatocellular carcinoma is one of the leading causes of death in cancer patients. Well known risk factors implicated in etiology of hepatocellular carcinoma are chronic hepatitis B and C and hepatic cirrhosis. In the last years, due to the rising incidence of obesity and diabetes worldwide, non-alcoholic steatosis, non-alcoholic fatty liver disease and type 2 diabetes are newly described risk factors.

Donadon has focused his studies on patients with hepatocarcinoma and has shown that metformin significantly reduces the risk of hepatocarcinoma in diabetic patients, compared to patients treated with sulfonylureas or insulin, and also reduces the risk of hepatocarcinoma in patients with diabetes and chronic liver disease [36–39].

There are several meta-analyses supporting this data, for example a 31% incidence reduction of pancreatic and hepatocellular carcinoma for patients using metformin was reported by a meta-analyses of 11 trials [40]. Another meta-analysis evaluating 37 trials of patients with colorectal, pancreatic, breast and hepatic cancer, reported a reduced incidence of cancer in patients using metformin, comparing with non-users [41].

One meta-analysis stated that metformin does not significantly reduce the risk of hepatocellular carcinoma. This meta-analysis excluded all the studies with time-related biases [42, 43].

3.2 Metformin in colorectal cancer

Colorectal cancer is increasing in incidence and mortality worldwide, especially in countries with low and middle income, but also in high developed countries mainly due to life style.

The first data that reported the relationship between metformin and colorectal cancer risk emerged in 2004 and since then numerous studies have evaluated this

association and had different outcomes, reporting a decrease risk, an increased risk or no association [43, 44].

The first clinical trial that examine the chemopreventive effect of low-dose metformin on metachronous colorectal adenoma/polyp formation, was conducted in 2016, and the observation was that Metformin suppress the formation of metachronous colorectal adenoma/polyp [45].

Another study investigating the use of Metformin as chemopreventive therapy was performed in 2018 on a small number of patients without diabetes, and showed that metformin is reducing the risk of developing polyps. The adverse events were mild and with no differences between groups [46].

3.3 Metformin in breast cancer

A meta-analysis that included 11 clinical trials of patients with breast cancer, reported a 65% improvement in overall survival for patients with breast cancer and diabetes that are treated with metformin [47].

There are also studies suggesting that the use of metformin is changing the type of cancers diagnosed in patients with diabetes. For example, a study conducted by Berstein reported that in patients using metformin, breast cancer is much more frequent, especially the progesterone receptor positive-type [46], and another study reported that triple negative-type is less common [47]. Other data suggests that response rate is higher in diabetic patients with breast cancer receiving neo-adjuvant chemotherapy and metformin, comparing with those not receiving metformin [48].

3.4 Metformin in renal cancer

Kidney cancers incidence is increasing mainly due to the increasing rates of hypertension and due to the improvement of imaging techniques, because kidney cancers are most often asymptomatic. Renal cell carcinoma is the most common type of kidney cancer.

There are several studies reporting that patients with renal cancer and diabetes have a poor prognosis, and that diabetes has a negative impact on survival of these patients [49]. Also some articles suggest that type 2 diabetes may be an independent risk factor for renal cancers [50].

A meta-analysis performed in 2017 which included 8 publications on kidney cancer showed that metformin could improve the survival of renal cancer patients, especially for patients with localized renal cell carcinoma, and concluded that further investigation is needed regarding the effect of metformin on patients with localized and metastatic renal carcinoma in order to exclude disease heterogeneity [51].

3.5 Metformin in lung cancer

Lung cancer is the leading cause of death all over the world in both sexes and despite the recent advances in therapy, the prognosis of these patients is still no satisfactory.

Regarding lung cancer, Mazzone et al. and Tan et al. reported that in patients receiving metformin the incidence of adenocarcinomas is higher comparing with other histopathological types, and that patients receiving metformin had a better response to chemotherapy [52, 53].

A meta-analysis conducted in 2017 reported that metformin demonstrates a significant improvement of overall survival and progression free survival of patients with lung cancer [54].

Although, numerous trials reported a reduction in cancer incidence in patients receiving metformin, there are recent studies on diabetic patients with breast, endometrial, prostate and renal cancer receiving metformin that suggests no association between the use of metformin and cancer incidence [55].

For prostate cancer, studies and meta-analysis showed that diabetes may reduce the risk of prostate cancer [56], but also showed that patients with diabetes and prostate cancer have higher rates of mortality and relapse after prostatectomy [57, 58]. All these results are in conflict with other studies that reported that metformin may reduce the risk for prostate cancer and may improve survival [59, 60].

4. Metformin: combination with antineoplastic drugs

Taking in consideration all the information available stating that metformin has a positive effect on cancer incidence and mortality, over the years numerous trial have evaluated or are underway to evaluate the combination of metformin with different antineoplastic drugs in breast, endometrial, prostate, lung, pancreatic and colorectal cancers.

4.1 Metformin: combination with chemotherapy

There are numerous chemotherapeutic drugs evaluated in combination with metformin. For example doxorubicin, cyclophosphamide, docetaxel, trastuzumab, exemestane, letrozole, carboplatin, 5-flurouracyl.

Combination of 5-fluorouracyl and metformin showed a modest activity in patients with colorectal cancer [61], but when used as chemopreventive treatment in monotherapy, metformin showed a reduced incidence of colorectal metachronous adenoma or polyp [45].

Metformin in combination with medroxyprogesterone acetate in endometrial cancer and atypical endometrial hyperplasia, showed a complete response rate of 14% in endometrial cancer and 81% in atypical endometrial hyperplasia and a good clinical profile with no severe adverse events [62].

For patients with diabetes and breast cancer receiving neo-adjuvant chemotherapy and metformin, Jiralerspong et al. reported a superior rate of complete pathological response [63].

In patients with prostate cancer the combination of bicalutamide and metformin may reduce cancer cells growth rate; in androgen receptor positive cells (AR) the reduction of cell growth appear to be mediated by anti-proliferative effect, and in androgen receptor negative cells by pro-apoptotic effect [64].

4.2 Metformin: combination with targeted therapies

Targeted therapies are used with success in the treatment of many cancer types, but usually the disease becomes unresponsive to treatment and shows acquired resistance, and this is a challenge for clinicians. Preclinical and clinical data showed that the combination of metformin with targeted therapies have good results. Targeted therapies comprise mostly of kinase inhibitors. At present more than 35 different types of kinase inhibitors are approved by FDA [65].

First targeted therapy approved by the FDA, was Gefitinib, a molecule targeting epidermal growth factor receptor (EGFR) in 2003 for the treatment of patients with locally advanced and metastatic non-small cell lung cancer (NSCLC) after failure of platinum and docetaxel chemotherapy [66]. A high percent of patients receiving gefitinib have high response rate, but despite this, patients rapidly develop

resistance. Mechanisms involved in resistance to Gefitinib are activation of mTOR pathway and upregulation of insulin-like growth factor-1 receptor (IGF-1R), and taking into consideration the effect of metformin on mTOR pathway inhibition and IGF-1R pathway suppression, multiple studies started to evaluate this relationship. The result were that the addition to metformin to Gefitinib reduce proliferation and can revert resistance to gefitinib [67, 68]. Combination of metformin and Gefitinib also improve prognosis of patients with NSCLC, by increasing survival and by delaying resistance to targeted therapy [69]. At this moment, a phase II multicenter double blind trial evaluating gefitinib in combination with metformin as first-line treatment for patients with locally advanced NSCLC, is ongoing [70].

Sorafenib was approved in 2007 for treatment of advanced hepatocellular carcinoma, but showed low response rate and serious adverse events [71]. Combination of Sorafenib and other drugs was necessary in order to improve treatment efficacy. So far, data showed that metformin has the capability to increase sorafenib efficacy by reducing lung metastasis in patients with hepatocellular carcinoma. The mechanism of action of this combination is targeting the mTOR pathway [72].

Trastuzumab was approved in 1998 for the treatment of HER2-positive breast cancer. Combination of Trastuzumab and metformin in clinical trials conducted over the years, showed that metformin suppresses the proliferation of trastuzumab-resistant breast cancer cells and also have a cardio-protective effect, against cardiac events related to trastuzumab [73, 74].

Bevacizumab, inhibits VEGF-A, the result being inhibition of angiogenesis and regression of tumor vascularization, thereby inhibiting cancer growth. It was approved in 2004 in combination with chemotherapy for metastatic colorectal cancer and now it is used in the treatment of numerous cancer types-metastatic breast cancer, renal cell carcinoma, advanced epithelial ovarian cancer, non-squamous NSCLC [75]. Combination of metformin with bevacizumab was found to be effective in the treatment of ovarian cancer and metastatic non-squamous NSCLC in combination with chemotherapy [76, 77].

4.3 Metformin: combination with radiotherapy

Metformin in combination with radiotherapy may increase cancer response to treatment. As already mentioned, one of the mechanism of action of metformin is affecting complex I in the electron transfer chain, reducing the oxygen consumption and increasing the reactive oxygen species (ROS) within the cells, resulting in DNA damage [78]. Another proposed mechanism is activation of p53 by activating AMPK, and as a result cell cycle arrest. Both, metformin and radiotherapy can activate p53 and stop cell proliferation [79]. There are several articles and case reports, showing a better response for patients receiving radiotherapy and metformin, comparing with those without metformin in: esophageal cancer, rectal cancer and head and neck carcinomas [80].

5. Conclusions

Many studies reported a reduced incidence of cancer in patients receiving metformin in standard dose, but also these trials have limitations: most of the trials were retrospective, others included both patients with invasive and non-invasive neoplasms, others trials did not exclude patients exposed to other antidiabetic treatments, all these findings being responsible for potential biases.

In general, chemopreventive agents are used as long term therapies. Metformin meets all necessary criteria as a long term chemopreventive agent, because it is safe,

has a well-known mechanism of action, it is well tolerated with few adverse effects and it is cost effective.

Based on the available information, we can conclude that metformin is reducing cancer incidence and mortality, is increasing tumor response when used in combination with different types of cancer therapies, either chemotherapy, targeted therapies or radiotherapy, is improving the outcome of cancer patients, and can be used in cancer prevention.

Clinical trials which evaluated the effect of metformin in combination with different types of antineoplastic treatment included only patients with diabetes, therefore clinical trials evaluating the effect of metformin in non-diabetic population are needed in order to explore the benefit of metformin and also to evaluate the adverse events of combinations compared with monotherapy in this particular population.

Conflict of interest

Authors report no conflicts of interest.

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