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Nephroprotection and chemotherapy sensitivity impact of metformin during cisplatin therapy; an updated review

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ABSTRACT

Chemotherapy has been accepted as the most common choice for cancer treatment. However, chemotherapy-induced toxicity and chemotherapy resistance are the two challenging barriers to the treatment. Metformin is a safe, inexpensive, and the first line drug to treat type II diabetes. It has also a significant anti-tumor effect with a selective cytotoxic efficacy on cancer stem cells. It also has renoprotective efficacy. The current study contributes to incorporating metformin to chemotherapeutic agents to develop treatment efficiency and reduce the chemotherapy-induced side-effects (such as toxicity and resistance) and also to benefit the nephroprotective impact of this drug.

Implication for health policy/practice/research/medical education:

The current study contributes to incorporating metformin with frequently prescribed chemotherapeutic agents to develop treatment efficiency and reduce the chemotherapy-induced side-effects (such as toxicity and resistance), preventing cell proliferation, tumor growth, angiogenesis, metastasis, simulating apoptosis, targeting NF- κ B pathway, nephroprotection and anti-oxidant activity.

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Introduction

Chemotherapy has been accepted as the most common choice for cancer treatment. However, chemotherapy-induced toxicity and chemotherapy-resistance are the two challenging barriers to the treatment of malignancies, which may lead to cancer reappearance, cancer development, and secondary toxicity in other healthy tissues, particularly in kidneys, ears and brain. Therefore, it is crucial to discover adjuvant medications for patients with malignancies.

Metformin is a safe, inexpensive, and is the first line drug to treat type II diabetes and other metabolic diseases. It has also a significant anti-tumor effect with a selective cytotoxic efficacy on cancer stem cells (CSCs), particularly in breast, prostate, lung, pancreatic and ovarian cancers. Anti-tumor action of metformin might be accompanied by different effects including anti-inflammatory, anti-angiogenesis, mammalian target of rapamycin (mTOR) signaling pathway inhibition and AMP-activated protein

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kinase (AMPK) activation. Metformin induces a cytotoxic effect on cancer cells and restricts tumor proliferation. However, metformin by itself is inadequate to abolish tumors entirely and still has not been shown, having a potent efficiency to reduce the tumors in a significant number of clinical trials. The current study contributes to incorporating metformin with chemotherapeutic agents to increase treatment efficiency and reduce the chemotherapy-induced side-effects (such as toxicity and resistance) and also decreasing nephrotoxicity of cisplatin by renoprotective impact of metformin. Metformin would also decrease the concentration of chemotherapeutic agents to reduce the possibility of toxicity and to extend the remission time. Cisplatin-based chemotherapy is the fundamental treatment in many types of cancers. Therefore, the combination of metformin and cisplatin would be a new feature of cancer treatment (1).

To assess the safety of metformin in combination with chemotherapy agents such as cisplatin, various clinical trials were conducted (2). Metronomic strategies indicated that metformin will have anti-angiogenesis and anti-tumor effects, as well as a low-toxicity profile if constantly administered in a regular schedule. This unique pattern for cancer treatment would manage therapy-associated complications (3).

Materials and Methods

For this review paper, we used several sources including; Google Scholar, Web of Science, PubMed, Embase, Scopus and directory of open access journals (DOAJ) and others. The search was conducted using combinations of the following keywords or their equivalents; chemotherapy, metformin, cisplatin, nephroprotection, reactive oxygen species, kidneys, tumor, nuclear factor (NF)- κ B, cisplatin cytotoxicity, AMPK signaling pathway, tumor growth, angiogenesis, metastasis, apoptosis, antioxidant and Kidney injury.

Cisplatin chemotherapy-resistance and metformin chemotherapy-sensitivity

Recent studies have supported that the cytotoxic effect of metformin depends on specific genetic agents, namely, liver kinase B1 (LKB1), tumor protein p53, nuclear factor (erythroid-derived 2) -like 2 (Nrf2), nuclear factor (NF)- κ B, and the tumor environmental condition such as glucose availability and hypoxia. Numerous studies have examined metformin in combination with cisplatin and stated different results.

Liver kinase B1 (LKB1) deficiency

LKB1-AMPK mutation: Liver kinase B1 (LKB1)-deficient tumor cells that have been medicated by metformin are unable to maintain the ATP balance and are more

sensitive to apoptosis consequently. Therefore, metformin therapy would be effective to remove tumor cells with a defective LKB1-AMPK pathway by its cytotoxic effect. A report showed that the defective LKB1-AMPK pathway with mTOR inhibitor such as rapamycin did not change the metformin effect on inhibition of signal transducer and activator of transcription 3 (STAT3). It also indicated that metformin can control the STAT3 pathway by LKB1-AMPK-independent mechanism. These findings proposed that the augmentation of cisplatin cytotoxicity property by metformin, might refer to the oxidative stress prevention that interrupts the STAT3/interleukin-6 pathways (4).

KRAS/LKB1 co-mutation: Stimulation of the Kirsten rat sarcoma virus (KRAS) mutations and interruption of the LKB1 tumor suppressor gene would contribute to maintaining the action of non-small-cell lung carcinoma (NSCLC). Metformin intensifies the effect of cisplatin against KRAS/LKB1 co-mutated tumors and might inhibit or postpone the cisplatin resistance by CSCs (5).

p53 mutation

The p53 gene is the most frequently mutated gene in half of the cancers in humans, particularly in breast, ovarian and squamous cell lung cancers. Metformin may be attractive in the treatment of these cancers by its cytotoxic action. Results of a study displayed that the effect of metformin, as a chemotherapy-sensitizer with cisplatin, relies on the p53 gene. When p53 exists, metformin will sensitize cells to cisplatin, and if the p53 expression is deprived in cells such as JARID1B-high and p53 knockout cells, metformin will not sensitize them to cisplatin, as a result, tumor cell will be resistant to cisplatin-metformin (6).

Nuclear factor (erythroid-derived 2) -like 2 (Nrf2)

DNA methylation plays a significant role in chemoresistance. An original report offered a basic assumption that metformin sensitizes endometrial cancer cells to chemotherapy by the abolition of isocitrate dehydrogenase 1 (IDH1)-induced nuclear factor erythroid 2-related factor 2 (Nrf2) expression complicated in DNA methylation. Thus, directing Nrf2 can be offered as a therapeutic approach for improving metformin-induced chemotherapy-sensitivity (7).

A study proposed that metformin can prevent cisplatin-resistance in tumor cells by Nrf2. Additionally, it is able to reduce the Nrf2 expression and resistance genes in later stages such as GSTA1 and ABCC1 by prevention of phosphoinositide-3-kinase/ protein kinase B (PI3K/Akt) and extracellular signal-regulated kinases1/2 (ERK1/2) (8). Wandee et al reported that metformin increased anti-proliferation, anti-migration and anti-invasive effects of cisplatin in cholangiocarcinoma cells, almost by the

AMPK-mTOR signaling pathway associated with the activation of p53-p21 and focal adhesion kinase down-regulation. More investigation in another study by the same authors showed that suppression of Nrf2-induced antioxidant enzyme expression causes stimulation of reactive oxygen species (ROS) and reduction of antioxidant, cytoprotective, and metabolic genes and finally enhances the cisplatin cytotoxicity by metformin (9,10).

Nuclear factor (NF)- κ B

Activation of the AMPK signaling pathway inhibits NF- κ B signaling (an upstream of inflammation) and metformin, as the AMPK activator, inhibits the inflammation caused by cisplatin and finally weakens chemotherapy -resistance in tumor cells (11).

Low glucose conditions

Compared with the cytoprotective effect of metformin under high glucose conditions, it enhances the cisplatin cytotoxicity in esophageal cancer cells cultured under glucose-deficiency conditions. The cytotoxic effect of metformin primarily influences cancer cells due to lack of nutrition and often happens in tumor cells instead of healthy cells which are associated with the decreased ATP production and the inhibition of AKT activation in malignant cells (12,13)

Hypoxia conditions

Hypoxia increases chemotherapy -resistance in various typical cell lines. Metformin might prompt chemotherapy -sensitivity of oral squamous cell carcinoma (OSCC) cells to cisplatin by NF- κ B inhibition that subsequently suppresses the expression of hypoxia-inducible factor 1 α (HIF-1 α). It leads to a reduction in hypoxia-associated gene products (14). It is also shown that low-concentration of metformin can augment the therapeutic effect of cisplatin in hepatoblastoma by HIF-1 α modulation. Conversely, metformin may facilitate resistance to cisplatin in hypoxic conditions by HIF-1 α (15). In this regard, a report stated that the anti-proliferative effect of metformin on cisplatin decreased under hypoxia conditions against normoxic conditions in endometrial cancer treatment (16).

Evidence

The effect of metformin on cisplatin cytotoxicity

Numerous studies have examined the combination of metformin and cisplatin, with different results. Many studies described that metformin increases the anticancer activity and acts as an adjuvant drug in cisplatin chemotherapy. However, few studies described that metformin reduces the anticancer activity and has antagonist effects on cisplatin cytotoxicity.

Adjuvant effect

A study demonstrated that metformin combined with cisplatin reduces the ability of CSCs to survive or live and causes the death of human ovarian cancer cells through the reduction of anti-apoptotic genes expression and increased expression of apoptotic genes (17). Metformin is stimulator of osteosarcoma cells to cisplatin by interrupting intracellular endpoints such as glutathione and ATP amount, reducing cell proliferation and prolonging cell cycle phases which may be accompanied or not with apoptosis stimulation. The anti-tumor effect of cisplatin may also conduct through also by cyclin-dependent kinase complexes inhibitors too (18). An in-vivo study revealed that metformin might potentiate cisplatin-induced cytotoxicity in xenograft models of ovarian cancer cells by preventing the proliferation, metastasis, and angiogenesis (19). Metformin can reduce AXL and TYRO3 expression, then interrupts ERK (extracellular signal-regulated kinase) and STAT3 (signal transducer and activator of transcription 3) pathways. It also reduces anti-apoptotic protein to hinder cell proliferation and reverse cisplatin resistance in cisplatin-resistant ovarian cancer cells. The combination of cisplatin and metformin inhibits proliferation, infiltration, and migration of malignant cells in human nasopharyngeal carcinoma cells. The expression of matrix metalloproteinase 7 and 9 will reduce with increasing metformin dosage, while tumor suppressor gene E-cadherin, phosphatase, and tensin homolog (PTEN) mRNA levels considerably will increase (20, 21). In a recent report, it was shown that metformin and caffeic acid may control one of the cancer hallmarks named "tumor metabolic reprogramming" in human cervical carcinoma cells and consequently can increase the cisplatin cytotoxicity by cell cycle control in cancer cells and also during co-incubation of cancer cells with fibroblasts. Cancer cells may affect the metabolism of fibroblasts and even congregate stromal cells to conduct their progression by supplying lactate, as an additional carbon source for tumor metabolism. Metformin amplifies pyruvate decarboxylation conversion to Acetyl-CoA and represses glutaminase and malic enzyme. In fact, it supports the mitochondrial biosynthetic metabolism from the additional carbon source (22). A study on esophageal squamous cell carcinoma as the most common type of cancer in China, also showed that metformin has an anti-proliferation ability and reduces xenograft tumor proliferation considerably by decreasing protein expression such as ribosomal protein S6 kinase beta-1 (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1) (23).

The anti-apoptotic effect of surviving and AKT is related to chemotherapy resistance in some types of cancers. Another possible mechanism of metformin for increase

cisplatin cytotoxicity is the reduction of surviving and AKT expression via AMPK activation and mTOR signaling inhibition (24).

Antagonism: Metformin has antagonized the cisplatin cytotoxicity in many cancer cell models such as glioma, neuroblastoma, fibrosarcoma, and leukemia cell lines through AMPK-independent up-regulation of Akt, autophagy or ERK (25), and in MKN-45 cell line by mTOR pathways (26). Thus, the collaboration of metformin with cisplatin to amplify chemotherapy-sensitivity relies on the type of cancers.

In a more recent study, it is shown that metformin protects cancer cells from cisplatin against compound C, as an AMPK activator. These findings suggest that cisplatin-induced AMPK activation and also mTOR pathway inhibition may lead to autophagy that defends cancer cells from cisplatin-induced cell death (27). However, findings a retrospective study also proposed that patients with lung cancer did not improve from metformin treatment due to increasing the expression of ERK1/2, AKT, and c-poly (ADP-ribose) polymerase (c-PARP) (28).

Conversely, metformin protected OSCC cells against cisplatin toxicity because the reduction of cisplatin-DNA adducted construction via a significant enhance in glycolysis and intracellular nitrite reductase levels (29).

Metformin effect on cisplatin induced-toxicity in healthy cells

One limitation of cisplatin administration is its toxicity in healthy tissue. The newest studies indicated that metformin might prevent normal cell apoptosis from cisplatin-induced toxicity especially in ears and kidneys. Moreover, metformin mitigates the side effects of cisplatin therapy such as neurotoxicity, nephrotoxicity, cognitive impairment, (30) and brain damage (21). A more recent study showed that metformin modified cisplatin-induced hepatotoxicity by a decrease in oxidative stress, reducing caspase-3, MAPK activation, and reduction of NF- κ B level by peroxisome proliferator-activated receptors (PPAR)-dependent pathways (31). However, in another report, the pretreatment of metformin could significantly weaken cisplatin-induced acute renal failure and inflammation by increasing both AMPK α phosphorylation and autophagy stimulation in kidneys after cisplatin therapy (32). In another study, it is shown that metformin could weaken ROS production and acts as an antioxidant, while could not influence cisplatin-induced kidney injury and histological abnormalities. Both metformin and cisplatin have structural analogs and cationic charges with substrates of organic cationic transporters. Finally, metformin might increase the renal accumulating of cisplatin, therefore it may be unable to inhibit cisplatin-induced nephrotoxicity (33).

Nano-compound based on the metformin-cisplatin combination

Nano-cubosomal metformin-cisplatin combination enhances cytotoxic efficiency in colorectal cancer cells compared to unformulated cisplatin through inhibition of AMPK/mTOR and AKT /mTOR pathways due to additional mTOR inhibitors (metformin) and energy depletion. Moreover, drug-loaded nano-cubosomes cause a substantial intensification in ROS levels, NADPH oxidase, lactate dehydrogenase inhibition, and a significant increase in caspase-3 (34).

Polymer-cisplatin nanoparticles showed the highest anticancer effectiveness between all treatment groups due to core-membrane nanoparticles co-encapsulated with cisplatin (conjugated with polyglutamic acid (PGA) as anionic PGA- cisplatin) and metformin (as cationic polymer called polymer) and the synergistic effect of these two complexes (35).

Conclusion

The current study contributes to incorporating metformin with frequently prescribed chemotherapeutic agents to develop treatment efficiency and reduce the chemotherapy-induced side-effects (such as toxicity and resistance), preventing cell proliferation, tumor growth, angiogenesis, metastasis, simulating apoptosis, targeting NF- κ B pathway, nephroprotection, anti-oxidant activity, targeting CSCs, and diminishing multidrug resistance. Numerous studies have examined metformin in combination with cisplatin and reported different results. Although many studies described that metformin increased the anticancer activity and act as an adjuvant drug on cisplatin chemotherapy, some other studies described that it reduced the anticancer activity and had an antagonist effect on cisplatin cytotoxicity.

Authors' contribution

MAS and SM searched the data and prepared the draft of the manuscript. RV and AM edited the manuscript. Secondary edit of the paper by SJK and SE. MAS conducted final check, final edit and finalized the manuscript. All authors read and signed the final manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

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

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