Metformin - its anti-cancer effects in hematologic malignancies

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Abstract

The main anti-diabetic effect of metformin mediated through stimulation of adenosine monophosphate (AMP)-activated protein kinase (AMPK) is the inhibition of hepatic gluconeogenesis and triggering glucose uptake in skeletal muscles. Additionally, some new pathways, besides the AMPK activation, were discovered, that can explain wide-range properties of metformin. All these properties are now attracting the attention of researchers in the fields other than diabetes and the drug has been reported to have anti-cancer, immunoregulatory and anti-aging effects. Among others, the beneficial effects of metformin in hematological disorders like leukemias, lymphomas, and multiple myeloma were reported. Despite a great progress in therapy, these diseases are still incurable in most cases. Thus, there is an urgent need to discover novel, less toxic and more effective drugs especially for older or chemotherapy-resistant patients. In this review article, the current findings on the anti-cancer effect of metformin together with underlying possible mechanisms in blood cancers are discussed. However. to evaluate precisely these promising effects of metformin, more studies are required, because many of the published results are preclinical.

Introduction

Metformin is a biguanide derivative that has been used as an anti-diabetic drug and has been known for nearly one century. Biguanides were initially derived from a plant, Galega officinalis, and were indicated to be rich in guanidine. Guanidine was shown to have hypoglycemic activity in animals, however it was toxic in clinical use.[1,2] Thus, in 1929, new biguanides with ability to reduce serum glucose levels were synthesized, among them dimethyl biguanide (1,1-dimethyl biguanide hydrochloride or metformin). In contrast to sulfonylureas, metformin fails to induce insulin secretion but inhibits the release of glucose by the liver and increases muscle glucose uptake.[1,2] Additionally, metformin was proved to be safe and not expensive. When it was used as a monotherapy, hypoglycemic side effects were not observed and a favorable effect on body weight was noticed.[3,4] In the 1990s, the United Kingdom Prospective Diabetes Study has shown that regardless of glycemic control, metformin is able to reduce the risk of myocardial infarction and decrease all-cause mortality in diabetes patients.[5-8] As a result, according to the international experts guidelines, metformin is now recommended as the first-line treatment for type 2 diabetes (T2D) and is the most frequently administered drug to treat this disease.[1,3,9]

Results of further research revealed the benefits of metformin in people with diabetes other than glycemic control. Interestingly, metformin was shown to reduce the risk of cancer. Many epidemiologic analyses have reported that metformin may improve prognosis of patients with different types of malignancies and even may prevent tumor initiation.[1,9,10] Evans *et al*.[8] noted as first that patients who were treated with metformin had a low risk of developing cancer. Next, a lots of studies in T2D patients have shown that metformin therapy is correlated with a reduced risk of numerous malignancies such as prostate cancer,[11,12] lung cancer,[13,14] head and neck cancer,[15] breast cancer,[16] pancreatic cancer,[17] colorectal cancer,[18] ovarian cancer[19] and liver cancer.[1,20.21]

Among other things, there is also medical evidence that supports the benefits of metformin in patients with blood cancers. Unfortunately, many of the studies in this field provide only preclinical data, while heterogeneous results have been reported across different clinical trials. Therefore, more clinical and epidemiological studies are required to support the role of metformin as an anti-cancer agent. This review article presents the current findings on the anti-cancer effect of metformin in myeloproliferative and lymphoproliferative disorders. This drug may be a novel and less toxic therapeutic option for hematological malignancies and should attract the attention of researchers and physicians.

Mechanisms of metformin action

Metformin is indicated for patients with T2D, which is characterized by hyperglycemia due to tissue resistance to insulin and its low secretion. The main mechanism of metformin action is the reduction of the rate of hepatic glucose production and an increase of insulin sensitivity in liver as well as intensification of glucose absorption in muscles.[22-24] Together, these actions reduce blood glucose level with very little possibility of inducing hypoglycemia.[25] An activation of anaerobic metabolism in the intestinal wall may be additional anti-glycemic effect of metformin.[26-28]

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The most significant place of metformin action is mitochondrion. Its main function is ATP synthesis by oxidative phosphorylation. This process leads to the production of energy via oxidation of nutrients and creation of electron chemical gradient through the mitochondrial inner membrane. This gradient is used as an energy source that allows the ATP synthesis, heat production and transport of ions.[29] Simultaneously, reactive oxygen species (ROS) are produced in mitochondria and may be toxic for cells and be responsible for DNA, protein and lipid damage. It may lead to oxidative stress and mitochondrial dysfunction, that has been reported to cause an insulin resistance in tissues.[30-32]

As far as a molecular mechanism is concerned, metformin appears to inhibit mitochondrial respiration at the level of respiratory chain complex I.[33] The generally accepted mechanism of its action is stimulation of adenosine monophosphate (AMP)-activated protein kinase (AMPK). An increase in the AMP:ATP ratio in situation of metabolic stress such as hypoxia and glucose deficiency, stimulates directly the AMPK activation and can be considered as an indicator of energy level in cells.[30,34,35] Metformin is accumulated within the mitochondrial matrix in hepatocytes and influences complex I of the respiratory chain [33,36]. Inhibition of this complex I results in an ATP reduction and an increase in ADP and AMP levels, and this finally leads to the AMPK stimulation [33,36,37]. AMPK blocks gluconeogenic gene transcription. Furthermore, it inhibits lipogenesis, which enhances insulin sensitivity.[23,38,39]

Recently, some new pathways of metformin action, besides the AMPK activation, were discovered. The decrease in cellular energy level can directly inhibit the gluconeogenic process. An increased AMP level may inhibit the adenylate cyclase, resulting in lowering of cyclic adenosine monophosphate (cAMP) production. As a result, the activity of protein kinase A (PKA) and its targets, including cyclic AMP response element binding (CREB), are reduced. Additionally, metformin inhibits the activity of glycerol-3-phosphate dehydrogenase (mGPD) and prevents glycerol usage in gluconeogenesis. The cytosolic redox state is increased, which diminishes the use of lactate as a gluconeogenic substrate.[23,40-42] Additionally, metformin may stimulate the secretion of GLP-1 (glucagon-like peptide-1) that enhances glucose-dependent insulin release from the pancreas and leads to a glucose level reduction.[43,44]

Increased risk of cancer in diabetes

The increased risk of carcinogenesis in patient with T2D was reported by many authors.[45-47] There are many risk factors that are similar for T2D and cancer. These factors include obesity, hyperglycemia, hyperinsulinemia, and chronic inflammation due to overweight and body fat mass.[46,47] Obesity and insulin resistance have been connected with an increased risk of several cancers, including solid tumors and hematologic disorders. There are both prospective data and meta-analyses supporting the association between an increased BMI and the increased risk of both lymphoid and myeloid neoplasms.[48-51] Similarly, such a correlation was observed for T2D and the increased risk of non-Hodgkin lymphomas (NHL), leukemias and multiple myeloma (MM).[52,53] Additionally, high glucose levels was reported to correlate with the increased risk of mortality in the course of MM, NHL, and leukemia.[54]

The important mechanisms connecting obesity and insulin resistance with cancer include the changed lipid signaling, effects of adipokine and inflammatory cytokine, as well as activation of PI3K/Akt/mTOR and RAS/RAF/MAPK/ERK pathways.[45] Obesity and insulin resistance or T2D may pre-dispose to blood cancers via activation of these different pathways, and especially the aggressive and chemo-resistant types of cancers are observed in patients with underlying metabolic syndrome.[45,55]

Metformin and its anti-cancer activity

Indirect mechanisms of metformin effects

Metformin is able to mediate its anti-cancer effects in both in an indirect and a direct manner. The indirect mechanisms result from inhibition of tumor growth connected with high-fat diet and hyperinsulinemia that are cancer risk factors as mentioned above. It is reported that insulin and insulin-like growth factor 1 (IGF-1) can promote tumorigenesis by stimulating the cell proliferation.[23,56] Metformin, through the lowering of blood glucose and insulin levels as well as insulin receptor activation in tumor tissue, is able to influence the survival of cancer cells. This mechanism is similar to that causing tumor growth inhibition by dietary control.[57,58] Metformin is able to impair the enzymatic function of hexokinases that catalyze production of glucose-6-phosphate, as a result the use of glucose by tumor cells is inhibited.[59,60] Metformin is also able to affect the inflammatory processes that are reported to be involved in tumor progression. Inhibition of a transcription factor - the nuclear factor-κ B (NF-κ B) leads to diminished secretion of pro-inflammatory cytokines.[61] Moreover, metformin has been reported to stimulate the immune response to cancer cells.[23,62]

AMPK-dependent mechanisms of metformin effects

The direct anti-cancer activity of metformin is related to AMPK-dependent and AMPK-independent mechanisms.[63] In reference to this, the key effect of AMPK activation is the inhibition of downstream AKT/mTOR signaling, that is the main regulator of cell proliferation. Such an inhibition results in the suppression of cell growth.[29,64,65] Further, experimental research provides evidence that metformin, in an AMPK-dependent manner, may regulate the cell cycle through interactions with oncogenes and tumor suppressors such as c-MYC.[66] AMPK has also been reported to induce the cell-cycle arrest by Ser15 phosphorylation of p53 protein.[35,67] On the other hand, it was reported that metformin treatment forces a metabolic conversion in p53-deficient cells. Thus, the drug is selectively toxic to p53-/-cells and may reduce incidence of tumors in patients being treated with metformin. Using metformin in patients with p53-deficient tumors, which are often resistant to classical forms of chemotherapy or radiotherapy may be of importance as well.[35] It was also found that metformin can have an anti-folate effect that inhibits cancer cell growth, similarly to anti-folate chemotherapeutics.[68,69]

AMPK-independent mechanisms of metformin effects

Anti-cancer mechanism of metformin action may be also mediated by AMPK-independent mechanisms. It was reported that the drug can inhibit cell DNA damage by preventing ROS generation by complex I.[70] In the absence of AMPK, metformin is also able to influence AKT/mTOR via suppression of mTORC1 signaling.[71] Moreover, suppression of cyclin D1, which is an essential regulator of the cell cycle, was detected.[72] Such an inhibition is reported to be connected with a p53-dependent up-regulation of REDD1 that is a result of DNA damage response. REDD1, a negative regulator of mTOR, is a new molecular target of metformin.[73] Next, it was found that metformin up-regulates apoptosis and autophagy through BCL-2 pathway, which also leads to reduction of tumor growth.[74] This was mediated by inactivation of the Stat3 (signal transducer and activator of transcription 3) - Bcl2 pathway. This pathway is merely marginally deteriorated by AMPK knockdown, that indicated rather reduced contribution of AMPK. It was also described that metformin reduced glucose uptake in cancer cells and such an energy source leads finally to mitochondrial depolarization and apoptosis.[59,75] The possible anti-cancer effects of metformin are listed in Figure 1.

Metformin in hematological malignancies

These properties of metformin, such as anti-cancer and immunoregulatory effects, have been attracting the attention of researchers in fields other than diabetes. Among the different cancers analyzed, the beneficial effects of metformin in hematological disorders were reported. Metformin was investigated as a therapeutic agent in patients with leukemia, lymphomas, and multiple myeloma. Additionally, many studies have demonstrated the synergistic or additive effect of metformin with chemotherapeutics, which may be used in lower doses, minimizing the side effects of high doses.[45,76-78]

Metformin in the therapy of different types of leukemia

The AMPK/mTOR signaling pathway is involved in pathogenesis of blood neoplasms, thus metformin may be a new option for these cancers therapy. Additionally, metformin does not seem to influence the survival of normal hematopoietic stem cells.[79-81] Next, some oncogenes, such as the protein kinase BCR-ABL that is a hallmark of chronic myeloid leukemia (CML) and may be present in acute leukemias as well as Tax oncoprotein, which is crucial in the pathogenesis of HTLV human retrovirus infection and adult T cell leukemia, are stimulators of the PI3K/AKT/mTOR pathway.[1,81] Hence, metformin, via AMPK activation, is able to suppress the proliferation of acute and chronic leukemias cells. Many studies have been published recently confirming the beneficial effects of metformin on leukemic cells under both *in vitro* and *in vivo* conditions.

Vakana *et al.*[82] reported that AMPK activators, such as metformin and 5-aminoimidazole-4-carboxamide ribonucleotide, were able to stimulate the mTOR signaling pathway in BCR-ABL–expressing cells. The therapy with these agents was potent to suppress of CML leukemic precursors and Ph^+ ALL cells, even cells with T315I-BCR-ABL mutation. This mutation caused resistance to most of tyrosine kinase inhibitors used in the therapy of CML and Ph+ ALL. The cell lines were used in the experiments, however, the results obtained indicate that AMPK is an attractive target for the treatment of BCR-ABL–expressing blood cancers.[82]

Similarly to study by Vakana *et al.*[82] Shi *et al.*[83] analyzed the effect of metformin on immature blasts of acute lymphoblastic leukemia (ALL) with the BCR/ABL translocation. Additionally, the authors studied CML lines K562 (sensitive to imatinib) and K562R (resistant to imatinib) co-cultured with metformin. The results obtained demonstrated that metformin was able to suppress cell viability, induced apoptosis, and downregulated the mTORC1 signaling pathway. Additionally, metformin was shown to potentiate the anti-cancer efficacy of imatinib in Ph+ALL and CML cells, re-sensitizing the CML imatinib-resistance cells to imatinib. The experiments were performed in vitro, however the results obtained suggested that metformin might be a promising and attractive agent for the Ph+ALL or CML therapy and the continuation of the research is of importance.[83]

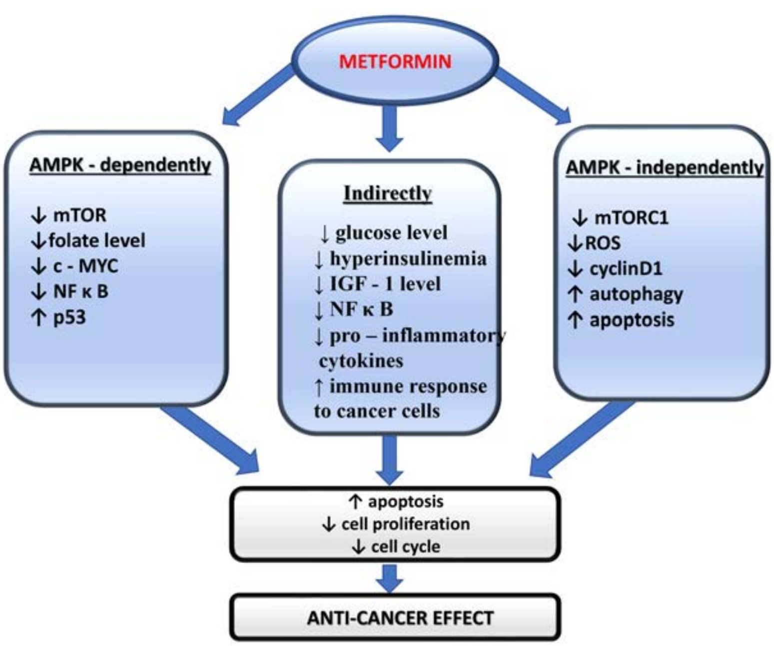

Figure 1. Anti-cancer effects of metformin.

Another study that proofs beneficial effects of metformin in lymphoblastic leukemia was presented by Rosilio *et al*.[84] The authors analyzed the effect of metformin, phenformin, and an AMPK activator - AICAR, on cells of human T cell acute lympoblastic leukemia (T-ALL). The experiments were performed in an animal model, on cell lines and blood samples from patients. The results demonstrated that all of these agents were able to suppress tumor metabolism and proliferation through the prevention of mTOR activation. The drugs under study did not influence the survival rate of normal T lymphocytes, thus displaying a specific anti- cancer effect. The authors observed synergistic effects on cell death when the analyzed substances were combined with dexamethasone, but less with doxorubicin, which are the drugs used in induction therapy of ALL.[84]

A very interesting study performed under *in vivo* conditions was presented by Ramos-Panafiel *et al*.[85] The authors determined the effect of metformin on the therapy of ALL patients with high levels of *ABCB1* treatment resistance gene expression and assessed its impact on overall survival. The group of 26 patients with ALL was treated by combining standard chemotherapy with metformin and compared with patients (no=76) receiving chemotherapy without metformin. The authors observed a benefit of adding metformin in the group of patients with high *ABCB1* gene expression. In the metformin group, the drug was a protective factor against early relapse and treatment failure.[85] Thus, metformin may be considered as a concomitant medication in chemotherapy for ALL patients.

The recently published results by Yuang *et al*.[86] determined the anti-leukemic activity of metformin combined with AraC in acute myeloid leukemia (AML). The experiments were done in AML cell lines and in animal xenograft tumor model to assess the effects *in vivo*. The authors found that metformin could synergistically sensitize AML cells to AraC by inhibiting the mTORC1/P70S6K signaling pathway.[86] Such synergistic effect of AraC and metformin may be a prospective therapeutic option especially for older patients with AML who cannot be treated by intensive chemotherapy.

Effect of metformin on AML cells was also analyzed by Sabnis *et al*.[87] They examined the combination of 6-benzylthioinosine (6-BT), a broad-spectrum metabolic inhibitor, and metformin in monocytic AML cell lines and umbilical cord blood cells. This combination resulted in high cytotoxicity of leukemic cells and was associated with inhibition of FLT3-ITD activated STAT5 and reduced c-Myc and GLUT-1 expression. The authors concluded that such combination might be a promising strategy for AML therapy [87]. These preliminary results are worth to be continued.

Anti-leukemic effects of metformin were also assessed in a specific subtype of AML - acute promyelocytic leukemia (APL). APL is characterized by the t(15;17) translocation and is treated with all-trans retinoic acid (ATRA) or arsenic trioxide (ATO) - based regimens. Huai *et al*.[88] demonstrated that metformin synergized with trans-retinoic acid, inducing the differentiation and apoptosis in leukemic blasts of cell lines. Asik *et al*.[89] investigated the effects of combination of a classic anti-cancer agent paclitaxel and metformin on HL-60 APL cell line. Such a combination significantly increased apoptosis of leukemic cells, so the authors suggested it could be a new option assessable for development of new treatment strategies for APL.[89] These studies may be a basis for further research in APL patients.

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western countries, with a median age in the moment of diagnosis about 70 years. Approximately 20% of CLL patients have type 2 diabetes. Bruno *et al*.[90] studied effects of metformin on CLL cells in an *in vitro* culture. The drug was administered to quiescent leukemic cells or during CLL cell activation, provided by co-culturing with CD40L-expressing fibroblasts. Metformin induced cell death of quiescent CLL cells and inhibition of cell cycle entry when CLL were stimulated. There was no effect on normal lymphocytes. Moreover, the drug combination experiments were performed, in which metformin accelerated the cytotoxic effects of anti-leukemic drugs - fludarabine and BCL-2 inhibitor.[88] Adekola *et al*.[91] demonstrated that treatment of CLL cells with HIV protease inhibitor ritonavir, caused toxicity comparable to that occurring upon glucose-deficiency. CLL cells resistant to ritonavir were sensitized by metformin co-therapy, possibly influencing the mitochondrial complex 1 action. The authors suggested further investigation of ritonavir and metformin for therapy of CLL patients.[91] Based on these preliminary results on CLL cells, the more precise analysis in CLL patients should be performed with this therapeutic option.

Several clinical trials on metformin alone or in combination with chemotherapeutics are proposed to assess the promising effect *in vivo* in patients with different hematologic malignancies. Description of these clinical trials is presented in Table 1.

Metformin in therapy of lymphoproliferative diseases

Lymphomas are malignant tumors of the lymphoid system. A base of the disease is a clonal expansion of lymphocytes, which are at different stages of development. Lymphomas are frequently diagnosed blood cancers with heterogenous course and different prognosis.

Shi *et al*.[92] were first to provide evidence on anti-tumor effects of AMPK activation in lymphomas. In their study, metformin induced a suppression of cell growth in both B-cell and T-cell lymphomas via negative control of the mTOR pathway. This suppression was a dose-dependent. Interestingly, the sensitivity of lymphoma cells to other anti-cancer agents, such as doxorubicin and temsirolimus, an mTOR Inhibitor, was enhanced by concomitant metformin treatment through the induction of autophagy.[92] There was also reported that an activation of p53 by suppressing murine double minute X (MDMX) by metformin in human lymphomas was able to cause apoptosis in a mechanism additional to inhibiting the mTOR pathway.[1] Quesada *et al*.[93] described the constitutive activation of mTORC2, NF-κB, p-Akt and the concomitant expression of IGF-1R in peripheral T-cell lymphoma. Interference of this pathway may provide a clinical therapeutic benefit, therefore the use of metformin as an inhibitor of mTORC2 and NF-kB in this type of lymphoma may be worth study.[93] Based on these results explaining the underlying mechanisms of metformin action in lymphomas, the further clinical trials may be undertaken.

Interestingly, it was also reported that metformin is able to reduce the risk of lymphoma incidence. Tseng *et al*.[94] analyzed whether the metformin use might affect the risk of non-Hodgkin lymphoma (NHL). They investigated the group of 610,089 newly diagnosed T2D patients who were followed up for NHL incidence. The results obtained revealed that the metformin use was associated with a lower risk of NHL compared with non-metformin antidiabetics.[94]

An analysis of patients with diffuse large B cell lymphoma (DLBCL), the most frequent type of B-lymphomas, and co-existing diabetes revealed that metformin added to first-line immunochemotherapy improved progression-free survival in comparison to other anti-diabetogenic drugs.[1,95] However, the results by Smyth *et al*.[96] published this year showed that metformin had no significant impact on survival in a retrospective population-based survey of all adults aged ≥66 years with DLBCL or transformed lymphoma treated with regimens containing rituximab. Wang *et al*.[97] investigated if metformin influenced outcomes in newly diagnosed DLBCL and follicular lymphoma (FL) patients. However, they found no evidence that metformin use was associated with improved outcomes in newly diagnosed DLBCL and FL.[97] Therefore, further studies are required to explain these inconclusive results.

Multiple myeloma (MM) is a lymphoproliferative disease of plasma cells of bone marrow that is still uncurable. Novel therapeutic options to improve outcomes in patients with MM are required. AKT involved in the PI3K/AKT/mTOR signaling path has high expression in progressive and resistant multiple myeloma. AKT contributes to many oncogenic functions in multiple myeloma which may be used in therapy. Pre-clinical data has reported the effectiveness of AKT inhibitors in MM, due to high expression of AKT in advanced and resistant MM and its contribution to multiple oncogenic functions in this disease.[98]

An interesting study focused on metformin in multiple myeloma was published by Zi *et al*.[99] The authors investigated whether metformin exerts an anti-myeloma effect in *in vitro* and *in vivo* xenograft models and explored the underlying mechanism. They found that metformin could suppress MM cells proliferation by inducing apoptosis and cell cycle arrest. Metformin inhibited the expression of IGF-IR, and PI3K, PKB/AKT and mTOR. Metformin had synergistic effect with dexamethasone but not with bortezomib. The authors have concluded that metformin stops MM cell proliferation via the IGF-1R/PI3K/AKT/mTOR signaling pathway and its use with dexamethasone may be investigated as a therapeutic option for MM patients.[99] However, the results provided by Jagannathan *et al*.[100] suggested that metformin was able to influence GRP78, a key driver of bortezomib-induced autophagy, thus to enhance the anti-myeloma benefit of bortezomib, that was in contrast to results of Zi *et al*.[99] and requires further explanation. On the other hand, Mishra *et al*.[101] reported that metformin specifically decreased IL-6R expression which is mediated via AMPK, mTOR, and miR34a. IL-6 signaling plays a crucial role in the

Table 1. Clinical trials investigating the antineoplastic effects of metformin in hematologic malignancies [based on https://clinicaltrials.gov].

Disease	Title of the study	Metformin/ other drugs	Status	Results
Acute lymphoblastic leukemia	Vincristine, Dexamethasone, Doxorubicin, and PEG-asparaginase (VPLD) and Metformin for Relapsed Childhood Acute Lymphoblastic Leukemia (ALL)	Metformin Vincristine Doxorubicin Dexamethasone PEG-asparaginase	Completed	14 patients enrolled Metformin dose 1000 mg/m^2/day 9 patients evaluable for response - 5 complete remissions, 1 partial response, and 1 stable disease104
Multiple myeloma Chronic lymphocytic leukemia	Metformin Hydrochloride and Ritonavir in Treating Patients With Relapsed or Refractory Multiple Myeloma or Chronic Lymphocytic Leukemia	Metformin Ritonavir	Active	
Acute myeloid leukemia	Metformin + Cytarabine for the Treatment of Relapsed/Refractory AML	Metformin Cytarabine	Terminated	
Chronic lymphocytic leukemia	A Pilot Study of Metformin Therapy in Patients With Relapsed Chronic Lymphocytic Leukemia (CLL) and Untreated CLL	Metformin	Active	
Solid Tumors Lymphomas	Metformin and Temsirolimus in Treating Patients With Metastatic or Unresectable Solid Tumor or Lymphoma	Metformin Temsirolimus	Completed	11 patients enrolled Metformin dose 500 mg 1,2,3 or 3 times per day 1 partial response, 5 stable disease105
Diffuse large B-cell lymphoma	DA-EPOCH-Rituximab/Metformin (RM) for Double Hit Lymphoma (DLBCL)	Metformin Immune-chemotherapy	Terminated	
Diffuse large B-cell lymphoma	Rituximab, Cyclophosphamide, Vincristine and Prednisone (R-CHOP) Plus Metformin in Diffuse Large-B-cell Lymphoma	Metformin Immune-chemotherapy	Unknown	
Non-Hodgkin's lymphomas	A Clinical Trial of Metformin in the Maintenance of Non-Hodgkin's Lymphoma Patients	Metformin	Recruiting	
Acute lymphoblastic leukemia	Metformin Reduce the Relapse Rate on Patients With B-cell Precursor (Ph+ Negative) Acute Lymphoblastic Leukemia	Metformin Chemotherapy	Completed	102 ALL patients Metformin dose 850mg every 8 h Metformin was a protective factor against early relapse and treatment failure[85]
Multiple myeloma	Clinical Activity of Metformin With High-dose of Dexamethasone in Relapse Multiple Myeloma	Metformin Dexamethasone	Unknown	
Multiple myeloma	Metformin and Nelfinavir in Treating Patients With Relapsed and/or Refractory Multiple Myeloma	Metformin Bortezomib Nelfinavir	Recruiting	

pathogenesis of MM and this novel finding may improve therapies targeting IL-6 signaling.[100]

Wu *et al*.[102] in a retrospective study conducted on 1240 MM patients assessed overall survival (OS) and disease status prior to death. According to the results obtained, diabetic patients had a shorter OS than non-diabetic subjects. As only the diabetic MM subjects were analyzed, Cox regression revealed that metformin predicted a longer OS, but use of insulin/analogues predicted a shorter OS [102]. Remarkable results of metformin effects in patients with monoclonal gammopathy of undetermined significance (MGUS) being a pre-myeloma stage were published by Chang *et al*.[103] The authors performed a retrospective analysis of patients in the U.S. Veterans Health Administration database diagnosed with MGUS. Data for 3287 patients were obtained, 2003 (61%) subjects were included in the final analytical group. Metformin users were defined as subjects who had been prescribed metformin for at least 4 years. The median follow-up time was 69 months, 463 (23%) participants were metformin users and 1540 (77%) were non-users. Among the metformin users, 13 (3%) patients had progression to MM, while in the group of non-metformin users 74 (5%) of patients progressed to MM. According to the results, it may be concluded that the metformin use was associated with a reduced risk of transformation to MM.[103-105]

Conclusions

Among different cancers, the beneficial effects of metformin in hematological disorders seem to be hopeful. Despite a great progress in therapy, these diseases are still incurable, so new drugs should be discovered. Metformin is minimally toxic; thus it may be a good option for older or chemotherapy-resistant patients. Additionally, it could be easily combined with other chemotherapeutic agents which may be used in lower doses, reducing the side effects. However, to evaluate these encouraging effects of metformin, more studies are required, because many of the studies in this field provide only preclinical evidence There are several clinical trials ongoing now in patients with blood cancers, but heterogeneous results require to be more specified. Despite these limitations, the metformin becomes a promising anti-cancer drug and the well-established clinical research should allow its wider use in oncological practice.

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