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IT'S TIME FOR NEW TREATMENTS IN PANCREATIC CANCER PATHOLOGY

Ramona Crişan [1, ✉]***, Mihaela Aldea*** [1]***, Gabriel Kacso*** [2]

[1] "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
[2] "Ion Chiricuţă" Oncology Institute, Cluj-Napoca, Romania

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Abstract

Background and aims*: The objective of this study was to conclude if there are enough scientific evidences to consider metformin as a potential treatment for pancreatic cancer.* ***Material and Method****: We performed a systematic search using PubMed and MedlinePlus up to September 2012. Reference list of relevant peer-reviewed literature were hand searched. Ultimately 15 articles were included.* ***Results****: Epidemiological studies had revealed that therapy with metformin was associated with 21% reduced risk for all types of malignancies, 31% reduction in overall summary relative risk, the median survival was longer: 16.6* vs. *11.5 months and the risk of death has decreased with 33%. In vitro it was proven that low doses of metformin block the stimulation of DNA synthesis and the growth of human pancreatic cancer cells. Prospective randomized clinical trials to confirm these data were already launched.* ***Conclusions****: These results raise the possibility that metformin could improve the poor prognostic of patients suffering from pancreatic cancer. Other clinical trials should confirm this hypothesis.*

key words: *metformin, pancreatic cancer, clinical trials, survival.*

Background and Aims

Pancreatic cancer is a real challenge for medicine. World-wide it contributes to more than 230,000 deaths annually. In US, pancreatic cancer (PC) is the fourth leading cause of death determined by cancer, for both men and women [1]. Despite all the efforts made trying to find new treatments, PC remains one of the most lethal malignancies with a 5-year survival rate of <5% and median survival duration of less than 6 months [1]. Surgical resection is the only chance for cure; even so, the five-year survival rate of patients who undergo pancreatectomy remains low [2]. However, the majority of the patients present with unresectable tumors. Patients with this type of cancer have few effective treatment options. Pancreatic cancer has no clear early signs or symptoms and is usually silent until the disease is well advanced. Risk factors that have been associated with pancreatic cancer include family history, chronic pancreatitis from any etiology: diabetes mellitus, smoking

✉ Str. Torentului nr 21, bl.T19, ap.16, Zalau, Jud Salaj; tel: 0744 145 212;
corresponding author e-mail: crisan_ramonica@yahoo.com

and obesity [3]. According to International Diabetes Federation 366 million people had diabetes in 2011 and by 2030 this will have risen to 552 million [3]. American Diabetes Association and European Association for the Study of Diabetes are both indicating metformin in combination with lifestyle changes, at the time of diagnostic. Metformin is the most widely used treatment prescribed for type 2 diabetes mellitus (T2DM) worldwide. It reduces blood glucose, reduces hyperinsulinemia associated with insulin resistance and it was also associated with decreased cancer risk in epidemiologic studies in diabetic patients. Preclinical studies have shown that metformin can inhibit the growth of cancer cells in vitro and in vivo [4] and clinical trials were already launched.

As the current therapies offer very limited survival benefits, novel therapeutic strategies to treat this aggressive disease are urgently required. Our aim was to perform a comprehensive literature review in order to establish if there are enough studies in the perspective of launching clinical trials using metformin in association with actual treatment for PC, or using metformin as a prophylactic therapy for patients at risk for developing PC. Available relevant studies were reviewed to conclude if metformin is a potential candidate for new therapeutic options and we searched the existent clinical trials using metformin in PC.

Material and Method

Studies were identified by a systematic search using PubMed and MedLinePlus up to September 2012. We searched using keywords: pancreatic cancer and metformin, metformin and apoptotic effect, pancreatic cancer growth and metformin. This review was restricted to English language publications. Initial search identified 80 abstracts which were evaluated for relevance and availability, 19 articles being considered potentially relevant. Ultimately 13 articles were selected.

Reference list of relevant peer-reviewed literature were hand searched to identify any appropriate articles. Another 2 articles that have been missed by electronic search were also included, so that finally 15 publications were reviewed in this article. Retrospective cohort studies, controlled trials were prioritized but also non-randomized trials, cohort studies, and case-control studies were considered. In addition, current clinical trials not yet published were searched on MedlinePlus using MeSh keywords „pancreatic neoplasma" and „pancreatic cancer".

Results

All the studies included in this review were divided into three categories: epidemiological studies, preclinical studies including in vivo and in vitro experiments and clinical trials.

Epidemiological studies

Several epidemiological studies have revealed the benefits of using metformin. A retrospective cohort study including a significant number of patients treated in UK showed that the therapy with metformin carried the lowest risk of developing colon or pancreas cancer, but it didn't had the same effect on other types of cancer. A reduced progression to cancer was also observed by adding metformin to insulin. Sulfonylureas

and insulin were not associated with a decreased risk of cancer [5]. A case-control study including patients with diabetes mellitus from a hospital in Texas has also revealed that diabetics receiving metformin treatment had a significantly lower risk of developing pancreatic cancer, compared with those who had not taken metformin or those who had taken thiazolidinediones [6]. Two epidemiological investigations in T2DM patients showed that taking metformin decreases the risk of developing malignancies compared with the patients treated with sulfonylureas or insulin [4]. One of them associated metformin therapy with a 21% reduced risk for all types of malignancies observing a dose-response relationship. The other one found a 31% reduction in overall summary relative risk in subjects taking metformin compared with other antidiabetic drugs. The association was more significant for pancreatic and hepatocellular cancer [4].

Since many studies have showed the role of metformin in preventing pancreatic cancer, the possibility that this drug could also influence the pancreatic tumoral cells should be taken into consideration. A retrospective cohort study in patients with diabetes and pancreatic malignancy reported that the median survival in metformin users is longer when compared to non-users: 16.6 *vs*. 11.5 months. Also the risk of death in patients who used metformin decreased with 33% compared to those who did not [7]. Furthermore another retrospective cohort study reported the median survival time to be 15.2 months in metformin users *vs.* 11.1 in non users [8].

In vivo and in vitro studies

A number of *in vitro* and *in vivo* studies explored the mechanisms of pancreatic tumoral cells growth and the factors that can interfere with this process, as summarized in Figure 1. Tumor cell accelerated multiplication depends on the stimulation of DNA synthesis from an extracellular impulse. This extracellular impulse is translated inside the cell through different receptors / signals. One of these receptors is insulin/insulin like growth factor (IGF-1) receptor which plays a critical role in pancreatic cancer development and it functions through AMP-activated protein kinase (AMPK) [9]. Metformin was proved to stimulate the activation of AMPK which is known as a cellular regulator in response to low energy in situations like hypoxia and nutrient deprivation. AMPK inhibits the mechanistic target of rapamycin complex 1 (mTORC1) function, which is a protein kinase and it induces cell cycle arrest and inhibits protein synthesis in cancer cells [10]. Metformin disrupts crosstalk between insulin and G-protein-coupled receptor (GPCR) signaling systems through AMPK in human pancreatic cancer cells. Metformin administration was associated with a reduced incidence and improved prognosis in cancer patients [11]. In vitro, metformin also prevented the stimulation of DNA synthesis induced by neurotensin and insulin in pancreatic tumoral cells PANC-1 and MIAPaCa-2, and by bradykinin and insulin in BxPC-3 cells. Insulin also enhanced GPCR agonist-induced growth, measured by DNA synthesis, and numbers of cells cultured in different conditions. Low doses of metformin were shown to block the stimulation of DNA

synthesis and cellular growth induced by insulin and GPCR agonists [12].

The next step was to see whether metformin could inhibit cancer growth in tumor xenografts in nude mice. One daily intraperitoneally administration of metformin had a great result. At the end of experiment the tumoral volume has reduced, so it was proved that metformin inhibits the growth of human pancreatic cancer cells xenografted in nude mice [11]. GPCR antagonist attenuates tumor growth in pancreatic cancer via a dual mechanism involving both the antiproliferative and antiangiogenic properties. GPCR antagonist, sustains growth inhibition *in vivo* by two different mechanisms: direct inhibition of cancer cell proliferation and by a previously unrecognized interference of the angiogenic properties of the HPAF-II tumor xenografts [13].

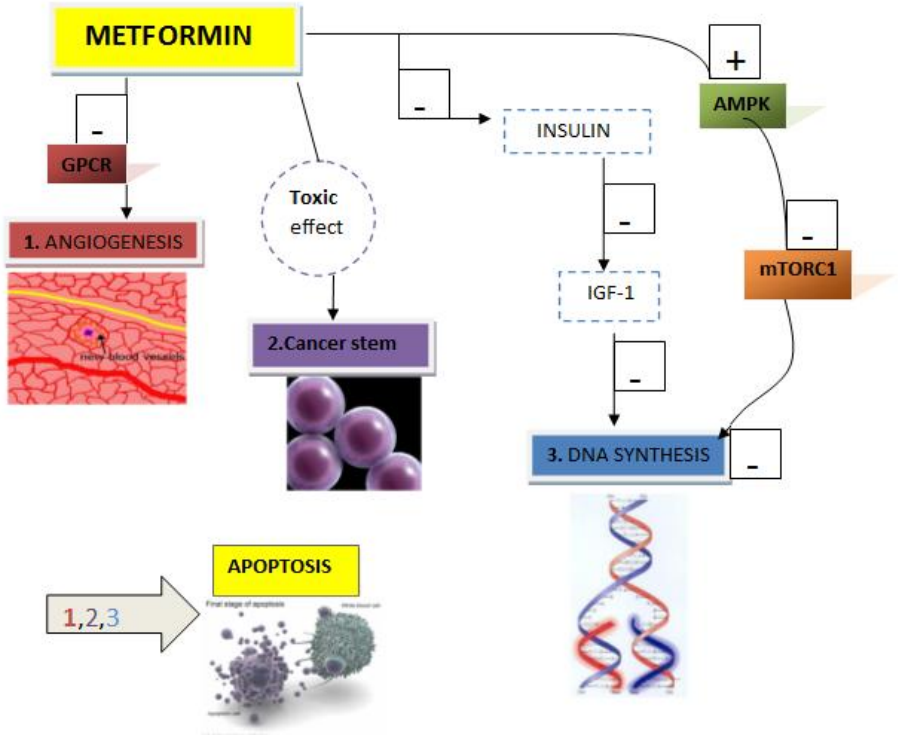

Figure 1. Possible pathways by which metformin interferes with pancreatic cancer development.

Clinical trials

It was proved that metformin is blocking at least one pathway involved in pancreatic tumor growth. In line with these observations, clinical trials were launched to study the effect of metformin in combination with other agents that inhibit separate pathways. A complete list of these trials is given in Table 1.

In a phase II placebo controlled study, investigators will use gemcitabine, erlotinib and metformin, or gemcitabine, erlotinib and placebo. Patients with locally advanced or metastatic pancreatic cancer will be randomized to receive the treatment. The aim of this study is to find potential combinations for more effective treatment. Another randomized phase II trial includes patients with metastatic pancreatic cancer treated with cisplatin, epirubicin hydrochloride, capecitabine, and gemcitabine hydrochloride together with metformin hydrochloride in

order to test their efficacy compared to cisplatin, epirubicin hydrochloride, capecitabine, and gemcitabine hydrochloride alone. Metformin was also included in a clinical trial associated with a therapeutic regimen which attacks the tumor compartment and the stromal compartment of the advanced stage IV pancreatic cancer. This innovative approach is trying to enhance the percent of patients who survive at one year. The investigators are using gemcitabine + mab-paclitaxel to collapse the stroma and propose the use of folfirinox, a non-cross resistant active regimen as a consolidation treatment. Metformin will be used after this consolidation in association with a less toxic targeted therapy selected by molecular profiling, because of the sustainable proofs that it is associated with better survival [Table 1].

Table 1. Ongoing clinical trials investigating metformin in pancreatic cancer.
(From ClinicalTrials.gov; October 2012).

Identifier	Title	Number of patients to be recruited	First end point	Description
NCT01210911	A Phase II, Randomized, Placebo Controlled Study to Evaluate the Efficacy of the Combination of Gemcitabine, Erlotinib and Metformin in Patients With Locally Advanced and Metastatic Pancreatic Cancer	120	August 2013	Gemcitabine at a dose of 1000 mg/m2 (iv, 30 minutes) will be given weekly, for 3 weeks,. Erlotinib will be administered at a daily dose of 100 mg Metformin/ placebo will be administered at a dose of 500 mg twice daily.
NCT01167738	A Randomized Phase II Study of Chemotherapy ± Metformin in Metastatic Pancreatic Cancer	82	January 2014	To assess the therapeutic activity of chemotherapy comprising cisplatin, epirubicin hydrochloride, capecitabine, and gemcitabine hydrochloride with versus without metformin hydrochloride in terms of 6-month progression-free survival in patients with metastatic pancreatic cancer.
NCT01488552	A Phase II Study of Induction Consolidation and Maintenance Approach for Patients With Advanced Pancreatic Cancer	30	January 2014	The Investigators have developed a therapeutic regimen which attacks both the tumor compartment and the stromal compartment of pancreatic cancer with advanced stage IV.
NCT01666730	A Phase II Study of Metformin Plus Modified FOLFOX 6 in Patients With Metastatic Pancreatic Cancer	43	July 2013	Metformin hydrochloride, leucovorin calcium, fluorouracil, and oxaliplatin, work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing. Toghether may kill more tumor cells and work in treating patients with metastatic pancreatic cancer.

Discussions

Compared with other types of cancer, where the data are inconclusive, there is enough information to accept that metformin has a beneficial role in the treatment of pancreatic cancer even though the exact mechanism involved remains undiscovered. Different types of studies were already completed and they concluded that using metformin has a positive influence for the prognostic of pancreatic cancer within different stages.

Side effects of metformin are generally well tolerated by patients but can vary from an individual to another. In addition, taking into consideration the low price of metformin and the wide application that it already has today, there are no impediments in launching new clinical trials in order to establish new therapeutic recommendations. This should be done as soon as possible because of the poor prognostic of pancreatic cancer that urgently needs a new approach.

Even though causal relationship between diabetes mellitus and pancreatic cancer is controversial, it was established that metformin has an indirect effect by lowering blood glucose [14], and it also has a direct effect interfering with tumor cells signaling. Life prognostic was ameliorated only by few months, but this time is important for the patients in the context of this lethal disease.

No clinical trial is completed yet and none has at least published some partial results. The purpose of mentioning the clinical trials currently ongoing was not to present their results but to underline the idea that the scientific community has already start to take metformin as a serious candidate for new treatment in pancreatic cancer.

A limitation of this review is that it included different types of studies: cohort studies and case-control studies, some of low quality. Another limitation of this review is the fact that most of them are retrospective studies.

Conclusions

Metformin is used as first line treatmeant in diabetes mellitus. Epidemiological studies have shown that it reduces the incidence of pancreatic cancer and it also ameliorates survival in these patients. In vitro and in vivo studies have shown that metformin has an indirect influence in pancreatic cancer cells growth by lowering blood glucose and also a direct effect interfering with several pathways of pancreatic cells development. A number of clinical trials were already launched in order to include this drug in the therapy for pancreatic cancer because patients need to benefit from these research findings. This field should receive special attention from researchers because the results could impact the poor prognostic for the patients suffering of pancreatic cancer. Other clinical trials should be directed to this drug and its influence for patients with pancreatic cancer.

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