

Metformin in Ovarian Cancer

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Abstract

Metformin after its discovery has found many wonders in many varied uses, poly cystic ovarian disease being already established one. It is now standard therapy in such condition. Many enchanting pathways are depicted leading to its many efficacies. In last decade its use in ovarian and other cancers is proposed. Before another such use is proved we can see the subject had grown bigger; hence a review seems to be worthwhile.

Keywords: Metformin; Ovarian cancer; AMPK; Stem cell

Introduction

Ovarian cancer has remained an enigma in abdominal tumours which shows no sign before it becomes too late to cure. Till date seventy percent of such cancer is diagnosed in late stage for any cure. This is partly because we know less about its causation. Many theories are proposed but exact cause is not found. Even it is not decided from where this tumour arises [1,2]. Epithelial ovarian cancer which constitute majority of such cancer is a heterogeneous entity where two types (I and II) are described. While type I is less aggressive and RAS related type II is predominantly TP53 mediated [3]. Stem cell described in such cancer depends on markers of "stemness" such as CD44, CD133, CD117, ALDH1A1, and EpCAM. Whereas there are many attempts to see characteristics of such stem cell in relation to NGF and FSHR [4-6]. Some other are trying to look at the metabolic reprogramming of cancer and cancer stem cells driven by genetic alterations which could be therapeutically targeted [7]. In such attempt metformin Gotlib et al. First proposed metformin in ovarian cancer in a preclinical study. It will be worthwhile to take closer look in the chapter of metformin in ovarian cancer.

Early development

Though there are many works on metformin in polycystic ovarian cancer in UK the subject of metformin's role in ovarian cancer has hardly any taker here except what could be found is a recent literature review by one group from Manchester [8]. And an observational quality of life trial recruiting patient in a study of the safety, tolerability and efficacy of metabolic treatments of advanced nonspecific cancer (METRICS) under Dr Angus Dalglish in Care Oncology Clinic at Harley Street, London. They are using Metformin with Atorvastatin, Doxycycline and Mebendazole. We will describe clinical trials later again.

Interestingly, epidemiologist Josie Evans and her group from Dundee University seem to be the pioneers of this subject working on it as early as 2005. They did a pilot observational study [9] to show that metformin may be associated with reduced risk of cancer in patients with type 2 diabetes and a biologically plausible mechanism exists. The

article became most popular and is cited 1100 times till date. This was followed by a Canadian cross-sectional study [10] with same finding shown in recent one [11].

AMPK and LKB1

Metformin (N, N'-dimethylbiguanide) is an anti-hyperglycaemic drug commonly used for the management of type-2 diabetes. It works by reducing liver glucose production and increase of glucose uptake by reduced insulin resistance peripherally in the muscle. Metformin via 5' adenosine monophosphate-activated protein kinase (AMPK) usually causes weight loss and reduced appetitenot weight gain and increased appetite. A recent breakthrough has found the upstream regulator of AMPK to be a protein kinase known as LKB1as was proposed by Evans et al. LKB1 is a well-recognised tumour suppressor. Activation of AMPK by metformin and exercise requires LKB1. Activation of the AMPK system by metformin inhibits growth of tumor cells through three different feedbacks; one positive and two negative pathways in a tissue-dependent manner. There is inhibition of mammalian target of rapamycin (mTOR) and fatty acid synthesis (FAS), but stimulation of the p53/p21 axis [12]. Other intermediary of mTOR (REDD1) and other pathways like cyclin D and FOXO3 are also described [13-15].

Other Mechanism of Anti-proliferative Activity

Miscellaneous pathways

Metformin has antitumor activity in monotherapy and also synergistically with other anticancer agents. Metformin stops proliferation of cell by by reducing the VEGF levelscontrolling neo vascularisation of tumour. At hormonal level it induces progesterone receptor thereby increasing the response to hormonal therapy [16]. glyoxalase I (GLO1), an enzyme that detoxifies methylglyoxal, is selectively overexpressed in the apoptosis-resistant cancer cells [17]. Metformin inhibits the expression of glyoxalase I, thus overcoming resistance to chemotherapy. It decreases in the concentration of human telomerase probably through the mTOR pathway. Metformin also reduces the activity of Akt and Erk kinases, key regulators of metabolism and progression of tumors. It abolished mTORC1 activation without over-stimulating Akt phosphorylation on Ser (473)

and prevented mitogen-stimulated ERK activation in cancer cells [18]. It also inhibits the formation of metastases.

Stem cell approach

Metformin down regulates the expression of a cancer-stemness marker CD44 and other stemness markers, including Nanog, Oct-4, c-Myc and, ALDH in these cancer cells [19]. Metformin significantly restricted the growth of ovarian cancer cell lines *in vitro*. This effect was additive with cisplatin. FACS analysis confirmed that metformin reduced ALDH(+) ovarian CSC [20]. Nevertheless, lot more to be detected before we know more about CSC and the CSC niche moleculogenetically and metabolically [21].

Metformin and immune system

Metformin is able to block the activation of NF- κ B, resulting in diminished cytokine-induced endothelial cell adhesion molecule expression. It may lead to decreases in chronic macrophage infiltration into the adipocytes of type 2 diabetics as well as lower the damaging consequences of autoimmunity. It can modulate the immune system outside of its anti-proliferative effects. It causes a significant enhancement of memory CD8 T cells which cause better tumor regression [22].

Clinical Scenario

Much can be said, deduced and seen in preclinical studies but drug efficacy and safety is a totally different matter when trial on human produce results which are only to valuable for patients. Early preclinical studies started just after the epidemiological studies and was continuing till recent times with almost equivalent efficacy [23,24] prompting many *in vivo* experiments. Say for example; Metformin can induce apoptosis in OVCAR-3 and OVCAR-4 cells by activating caspases 3/7, down-regulating Bcl-2 and Bcl-xL expression, and up-regulating Bax and Bad expression [25]. The induction of apoptosis by metformin was also enhanced by cisplatin and combination of these drugs did not modulate the expression of Bcl-2 family proteins in OVCAR-3 cell line, whereas the effect was enhanced in OVCAR-4 cell line.

In vivo study where A2780 ovarian cancer cells were injected intraperitoneally in different mice model studying growth and metastasis along with cisplatin [26] and paclitaxel [27] also showed its efficacy.

Ronald Buckanovich of University of Michigan is recruiting for a phase II clinical trial (NCT01579812) using metformin as an anti-cancer stem cell agent in ovarian cancer patients. Patients who plan to receive primary surgical debulking will initiate metformin therapy prior to surgery and then continue after surgery along with chemotherapy. Patients who will be treated neoadjuvantly will initiate metformin with chemotherapy prior to surgery and then continue both metformin and chemotherapy after surgery. Tumor specimens will be acquired for all patients at the time of primary surgery. The primary objective of this study will be to determine if metformin improves the recurrence-free survival (RFS) of patients relative to historical controls. Secondary objectives of this study will be: (a) to compare the amount of CSC in primary tumor specimens in metformin treated patients versus matched controls from our tumor bank, (b) to determine if metformin improves overall survival relative to historical controls, (c) to confirm the safety of metformin in non-diabetic ovarian cancer patients, and (d) as laboratory studies indicate

that metformin is most active in p53 mutant cells and p53 is mutated in ~50% of ovarian cancers, we will assess whether response rates correlate with p53 mutation status.

Seiko Yamada, University of Chicago is ready to recruit in NCT02122185 trial. Here patients will receive metformin hydrochloride postoperatively twice daily and standard chemotherapy regimen for 6 courses. Treatment for metformin hydrochloride continues for up to 2 years in the absence of disease progression or unacceptable toxicity. Another two like studies which have not recruited yet are in Fox Chase Cancer and in Center University Medical Centre Groningen. However, results will not be apparent before 2018.

Future Scope

At the end Professor Gotlieb of McGill University needs special mentioning who has some interesting revelation that establishes the chance of ramification of this subject and opens probable and newer enchanting routes of understanding of cause and path to cure in ovarian cancer. The organic cation transporter 1 (OCT1) experiment has shown. siRNA knockdown of OCT1 reduced sensitivity of epithelial ovarian cancer cells to metformin but interestingly, not to another biguanide, phenformin [27]. Drug uptake differences due to heterogeneity between primary human tumors with respect to OCT1 expression may raise doubt as to which one is the optimal biguanide.

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