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Role of metformin in radiotherapy and chemotherapy

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Abstract
There are several published reports showing antidiabetic agent metformin prevents the development of cancer and has an important role in the treatment of cancer. According to the recent studies, metformin is reported to enhance the effect of chemotherapy and radiotherapy, especially in cancer related to diabetes. But it is difficult to analyze the initiation of treatment as it has been recently started to be investigated. There is a need for prospective studies to investigate the efficacy and / or safety of metformin in combination with radiotherapy and chemotherapy in cancer treatment and in cancer patients.

Keywords: Metformin, radiotherapy, chemotherapy

Introduction

Diabetes mellitus (DM) and cancer are prevalent diseases with growing incidence. High morbidity and high mortality rates lead to high treatment costs and cumulative loss of manpower that are a heavy burden for society. In the recent years, despite significant advances in molecular genetics, the etiology and the pathophysiology of both DM and cancer are no fully understood. Diabetes Mellitus and cancer share similar risk factors that cannot be modified like ethnicity and some risk factor that can be modified by changes in lifestyle such as obesity, diet, alcohol, physical activity and smoking [1-3].

For over fifty years, the association between diabetes mellitus and cancer are known. Data from the meta-analyzes point at patients with DM that they are at risk for some types of cancer and also some types of cancer have been found to occur less often [1]. Although the mechanisms behind this are unknown, higher insulin sensitivity and increased insulin receptor expression in a cell was shown to contribute to the increased risk of malignant transformation by 2-6 fold [3-6]. In epidemiological studies, endometrium, liver and pancreatic cancers were found 2 times more; colon, breast, rectum and bladder cancers were found 1.2-1.5 times more than the normal population. Diagnosis of Diabetes Mellitus in pancreatic cancer patients at least 5 year before the initial disease suggest a positive relationship between DM and pancreas cancer. The reason behind lower incidence of prostate cancer in patients with DM is supposed to be a result of low testosterone levels and metabolic disorders related to diabetes [1]. There are still many questions that maintain complexity on whether presence of common risk factors for both DM and cancer or drugs used for DM treatment or pathophysiological mechanisms involved in the development of diabetes affect cancer development.

In the latest studies, increased relation between cancer and diabetes associated metabolic abnormalities and clarification of role of adenosine monophosphate protein kinase activation (AMPK) in cancer metabolism raised deep interest in metformin that acts by AMPK activation [4, 6.7]. There are several published reports showing antidiabetic agent metformin prevents the development of cancer and has an important role in the treatment of cancer [2]. Metformin shows its anticancer effect by reducing insulin-like growth factor (IGF) and insulin production, inhibiting HER2-mediated signaling, mammalian target of rapamycin (mTOR) signaling, angiogenesis. Indirectly, metformin causes cell cycle death and induces apoptosis [2,3,4,7]. Jung et al reported that Metformin which is used for type 2 diabetes treatment reduced tumor size and number significantly in breast, liver and pancreas cancer patients [4]. In Jiralerspong et al.'s study, 2592 neoadjuvant chemotherapy patients were enrolled. While they found that

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patients taking Metformin for DM (157 patients) showed % 24 pathological complete response to chemotherapy, it was found 8% in patients not taking Metformin. At last, they reported that metformin increases the rate of response to chemotherapy [3]. Metformin has been reported to inhibit growth of various cancer types both in vitro and in vivo [5-7]. In another work, Shell et al. combined HER-2-targeted agents and metformin. Besides synergistic effects, they were found to reduce cardiotoxic side effects by inhibiting AMPK activation in cardiac cells and lower morbidity and mortality rates were observed as a result [8]. Metformin may also prevent resistance in HER-2-based therapy and prolong life. Mammalian target of rapamycin (mTOR) signaling increases mostly in human cancer and mTOR-dependent protein activation is responsible for malignancy progression. It is also associated with poor prognosis and development of resistance [2,4,5].

According to the recent experimental and retrospective studies, DM patients using metformin responded to the radiation therapy better. It was indicated that use of Metformin in non-DM patients can increase the effect of radiation therapy (RT) [2.7]. Sanli et al. implanted Metformin to the treatment plan of lung, prostate, and breast cancer patients while undergoing RT. They indicated that Metformin has radio sensitizer property [6]. According to the recent experimental and retrospective studies, DM patients using metformin responded to the radiation therapy better. It was indicated that use of Metformin in non-DM patients can increase the effect of RT [2.7]. Sanli et al. implanted Metformin to the treatment plan of lung, prostate, and breast cancer patients while undergoing RT. They indicated that Metformin has radio sensitizer property [6]. Metformin is a direct radio sensitizer and reduces tumor stem cell fraction, proliferation, and tumor hypoxia indirectly. Also in certain genetic backgrounds such as loss of tumor suppressors genes like p53 and LKB1 [2,6].

Conclusion

In conclusion, limited pre-clinical and clinical studies support the use of metformin as an anti-cancer drug and radio sensitizer. In addition, it is known that metformin is reported to enhance the effect of chemotherapy and radiation, especially in cancer related to diabetes. But it is difficult to analyze the initiation of treatment as it has been recently started to be investigated. There are need for prospective studies investigating in which type of cancer Metformin will be used and in those cancers what will be the effectivity/reliability of Metformin.

Competing interests
The authors declare that they have no competing interest

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