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Can metformin change the prognosis of pancreatic cancer? Retrospective study for pancreatic cancer patients with pre-existing diabetes mellitus type 2

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ABSTRACT

Backgrounds: The effect of metformin on survival in patients with pancreatic cancer is controversial.
Aims: To investigate the beneficial effect of metformin in pancreatic cancer patients.
Methods: We retrospectively analyzed patients with pancreatic cancer and pre-existing diabetes mellitus type 2 who were treated at Severance Hospital (Seoul, South Korea) between May 2005 and December 2013.
Results: Among 237 enrolled patients, 117 patients (49.4%) were exposed to metformin. The median overall survival was 13.7 months for the metformin group versus 8.9 months for the non-metformin group ($P = 0.001$) In univariate analysis, metformin exposure, low serum carbohydrate antigen 19-9 levels (<1000 U/mL), small tumor size (≤20 mm), no tail involvement, good performance status (ECOG 0 vs. 1 or 2), and resectable cancer stage were associated with favorable survival outcomes (all $P < 0.05$). In multivariate analysis, in addition to low serum carbohydrate antigen 19-9 levels (<1000 U/mL) and resectable cancer stage, metformin exposure was significantly associated with longer survival with a hazard ratio of 0.61 ($P = 0.001$). Additionally, the cumulative duration of metformin use was significantly correlated with a favorable survival outcome.
Conclusion: Our findings supported that metformin exposure was associated with survival benefits in patients with pancreatic cancer and pre-existing type 2 diabetes mellitus, especially among those with an advanced cancer stage.

1. Introduction

Pancreatic cancer is the tenth most common cancer, accounting for approximately 3% of all cancers and 7% of cancer deaths in the United States [1]. Despite recent advances in molecular biology and the development of new chemotherapeutic agents, such as targeted cancer treatments, pancreatic cancer remains extremely lethal, with a 5-year survival rate of only 6% [2]. Surgical resection is the only potentially curative treatment modality for pancreatic cancer, but only 15–20% of patients are considered surgical candidates [3]. Novel strategies for primary prevention, early detection, and treatment are needed for this catastrophic disease.

The association between diabetes mellitus (DM) and pancreatic cancer has been recognized for a long time. Long-standing type 2 diabetes (more than 10 years) is considered an established risk factor for pancreatic cancer, increasing the risk thereof by 1.51-fold (95% confidence interval [CI] = 1.16–1.96) [4]. On the contrary, up to 80% of patients present with either new-onset (<2–3 years) DM or impaired glucose tolerance, as a manifestation of pancreatic cancer, at the time of diagnosis [5]. Several recent studies illustrated that metformin, one of the most widely prescribed drugs for type 2 DM, was associated with a lower incidence of pancreatic cancer compared to insulin or insulin secretagogues [6–8]. Although the anti-cancer mechanism of metformin is not fully understood, the principal mechanism of metformin's action is the alteration of the energy metabolism in the cell through the inhibition of mitochondrial oxidative respiration [9]. Also, the anti-cancer activity of

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metformin has been primarily attributed to its ability to directly activate the serine-threonine liver kinase B (LKB1)/AMP-activated protein kinase (AMPK) signaling pathway, which suppresses the mammalian target of rapamycin (mTOR) pathway [10]. Metformin additionally inhibit insulin-induced tumor growth by decreasing circulating levels of insulin and insulin-like growth factor-1 (IGF-1) [11,12]. Several in vitro studies discovered that metformin probably inhibits cancer cell proliferation, migration, and invasion and preferentially kills cancer stem cells [13,14]. These results were also supported by in vivo studies [15]. Considering the aforementioned findings, metformin can be regarded as a novel, promising, and well-tolerated drug for the prevention and treatment of pancreatic cancer.

To date, two retrospective studies have reported the effect of metformin on survival in patients with pancreatic cancer. One study by Sadeghi et al. revealed a survival benefit of metformin with an overall hazard ratio (HR) of 0.68 (95% CI = 0.52–0.89; $P = 0.004$) [16]. According to this report, the survival benefit of metformin use was statistically significant in non-metastatic stages. In another study by Hwang et al., metformin exposure during the peri-diagnosis period was not associated with a survival benefit in patients with an advanced stage of pancreatic cancer (locally advanced and metastatic stages) [17]. The effect of metformin on survival in patients with pancreatic cancer remains debatable. Therefore, the aim of this study was to investigate the anti-tumor effect of metformin in patients with pancreatic cancer and pre-existing DM.

2. Materials and methods

2.1. Study population

A total of 1339 patients with pancreatic cancer diagnosed between January 2005 and December 2013 at a single medical center, Severance Hospital at the Yonsei University Health System (Seoul, South Korea), were screened. Among these, 1102 patients were excluded based on the following exclusion criteria: no history of pre-existing type 2 DM ($n = 777$); follow-up loss of less than 1 months ($n = 102$); patients treated with just supportive care only ($n = 92$); incomplete records, including medication history ($n = 58$); diagnosis as metastatic lesion from another primary cancer ($n = 43$); absence of histological diagnosis to adenocarcinoma ($n = 27$); and any cancer diagnosed prior to or concurrently within a 5-year period ($n = 3$). Finally, 237 patients were analyzed.

2.2. Data collection

The demographic, clinical, and laboratory data of the study population were collected from medical records and reviewed meticulously. Medical records data including sex; age at diagnosis of pancreatic cancer; body mass index (BMI); Eastern Cooperative Oncology Group (ECOG) performance status; duration of DM; use of anti-diabetic medications such as insulin, metformin, sulfonylurea, thiazolidinedione, and dipeptidyl peptidase IV (DDP4) inhibitors; levels of Hemoglobin A1c (HbA1c) and Carbohydrate antigen 19-9 (CA 19-9) at the time of diagnosis; and pathologic and radiologic results were reviewed. In addition, clinical variables including the clinical cancer stage (resectable, locally advanced, and metastatic), primary tumor size, primary tumor site (head, body, or tail of the pancreas), treatment modality (surgery, chemotherapy, or radiotherapy), and date of death or last follow-up were reviewed.

Exposure to anti-diabetic medications, including metformin use, was determined from prescription records listed in electronic medical records or from self-reported records in the outpatient clinic. DM patients in our hospital were treated according to treatment guidelines for diabetes set by the Korean Diabetes Association. Since we focused on the anti-neoplastic effect of metformin on pancreatic cancer mortality, we investigated the cumulative duration of metformin use, beginning on the day of pancreatic cancer diagnosis. Metformin exposure was defined as the cumulative duration of metformin use at more than 1 month after diagnosis. Finally, the study subjects were divided into two groups, the metformin and non-metformin groups, according to their metformin exposure status, regardless of the use of other anti-diabetic medications.

2.3. Statistical analysis

The baseline characteristics of the two groups (metformin vs. non-metformin) were compared using Mann–Whitney U test for continuous variables and Pearson χ^2 test for categorical variables. Overall survival (OS) times were estimated using Kaplan–Meier plots. The log-rank test was used to compare survival time between the two groups. To identify factors predictive of survival, the Cox proportional hazards regression model was used for univariate and multivariate analyses. Variables displaying statistical significance were collected and evaluated in multivariate analysis. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using SPSS version 18.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the 237 enrolled patients, consisting of 117 patients in the metformin group (49.4%) and 120 patients in non-metformin group (50.6%), are summarized in Table 1. The patient population consisted of 237 patients. 157 patients were male and the median age of 66 (range 34–85) years. The average BMI was 21.8 kg/m^2, and the duration of DM before a diagnosis of pancreatic cancer was 5.0 (range 0.2–32.0) years. At the time of cancer diagnosis, 157 (66.2%) patients had received metformin, although only 117 patients (49.4%) had maintained metformin administration for at least 1 month (metformin group); the remaining 120 patients (50.6%) were included in the non-metformin group. The median primary tumor size was 40.0 (10.0–105.0) mm. In total, 53 (22.4%), 70 (29.5%), and 114 (48.1%) patients were diagnosed with resectable, locally advanced, and metastatic disease, respectively.

Between the metformin and non-metformin groups, there were no significant differences in baseline age, sex, BMI, HbA1c levels, tumor size, tumor site, stage, CA 19-9 levels, and performance status. The median durations of DM were 4.0 and 7.0 years in the metformin and non-metformin groups, respectively ($P = 0.010$). Among users of anti-diabetic medications, patients in the non-metformin group were more commonly treated with insulin (11.1% vs. 42.5%, $P < 0.001$) and less commonly treated with DDP4 inhibitors (17.9% vs. 8.3%, $P = 0.028$). Regarding clinical cancer stage, the metformin group included more patients of a resectable stage (29.9% vs. 15.0%, $P = 0.006$) and less patients of a metastatic stage (38.5% vs. 57.5%, $P = 0.003$).

3.2. Clinical outcome

The clinical outcomes of the enrolled patients are summarized in Table 2. Although patients in the metformin group received surgery more frequently than those in the non-metformin group (26.1% vs. 15.1%, $P = 0.006$), there was no difference in other treatment modalities, such as concurrent chemoradiation therapy (CCRT) and chemotherapy between metformin and non-metformin group.