JOP. J Pancreas (Online) 2013 July 10; 14(4):363-366.

HIGHLIGHT ARTICLE

Diabetes and Pancreatic Cancer

Highlights from the "2013 ASCO Annual Meeting". Chicago, IL, USA; May 30 - June 4, 2013

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Summary

There is great emphasis on early identification of high risk patients for developing pancreatic cancer in an attempt to reduce the burden of the fourth leading cause of cancer death in the United States. Abstracts presented at the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting highlighted and supported the relationship between pancreatic cancer and diabetes mellitus and Abstract #4039 showed that hemoglobin-A1c at the time of diagnosis correlates with disease stage and predicts survival among all stages of pancreatic cancer patients. Abstracts #4044 and #e15110 also presented in 2013 ASCO Annual Meeting showed that metformin treatment serves as a positive prognosticator, especially in patients with diabetes mellitus diagnosed within 2 years of pancreatic cancer and in stage 3 pancreatic cancer patients with diabetes mellitus.

Introduction

Statistics show that pancreatic cancer is the tenth most common cancer in the United States and is currently the fourth leading cause of cancer death [1]. Given its dismal prognosis, with a 5-year overall survival of only 5% [2], several attempts has been made to come up with appropriate screening methods in high risk populations. It is well established that smoking, obesity, family history of pancreatic cancer [3], chronic pancreatitis [3], pancreatic cystic lesions [4] and diabetes mellitus [5, 6] are risk factors for pancreatic cancer. Symptoms related to pancreatic cancer such as abdominal and back pain, jaundice, appetite and weight loss often occur at a late stage of the disease at which time a curative surgical approach is no longer an option.

Early studies have shown that up to 80% of patients with pancreatic cancer have either frank diabetes mellitus or impaired glucose tolerance [7]. Interestingly, this correlation could not be explained by impaired secretion of insulin, and it was thought that diabetes mellitus reflected pancreatic dysfunction as an early symptom of carcinogenesis [8]. This association between diabetes mellitus and pancreatic cancer attracted considerable attention, and several studies were designed to evaluate the value of using diabetes mellitus as a tool for screening, early detection and therefore improved prognosis in pancreatic cancer patients [9, 10, 11, 12].

Key words Diabetes Mellitus; Glucose; Metformin; Pancreas; Pancreatic Neoplasms

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What We Knew Before the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting?

Diabetes and Pancreatic Cancer: A Causal Relationship?

The Italian Pancreatic Cancer Study Group published a case control study in 1994 of 720 patients with pancreatic cancer. This study concluded that the increased prevalence of diabetes mellitus in these patients was likely related to the diabetes caused by the tumor [13]. Since that study several meta-analysis reported up to a two-fold risk of pancreatic cancer in diabetic patients [14, 15, 16].

Earlier this year, a nationwide population-based database in Taiwan was created to assess the correlation between gastrointestinal cancers and diabetes mellitus. The database included 39,515 patients with new onset diabetes with no previous diagnosis of gastrointestinal cancer. This study demonstrated that after a 7-year follow-up period, gastrointestinal cancers developed in 929 diabetic patients (2.35%) as compared to 1.42% in the comparison cohort that included 79,030 age and sex matched non-diabetic subjects [17]. Diabetes mellitus was associated with a 2.75-fold (95% confidence interval (CI): 2.51-3.02) higher risk of

developing a gastrointestinal cancer, including gastric, liver, colon, and pancreatic cancers (adjusted HR: 4.35; 95% CI: 2.93-6.47) [17]. Mizuno *et al*., published a retrospective study of 540 pancreatic cancer patients that showed that the prevalence of diabetes in different stages of pancreatic cancer was 45%, of which more than half were less than 2 years in duration [18]. Their data showed that even though the prognosis of pancreatic cancer patients complicated with diabetes was the same as patients with no diabetes, patients had better prognosis and survival if they were diagnosed in association with diabetes alone (median survival time: 20.2 months), compared to patients diagnosed by symptoms such as pain, jaundice, and/or appetite loss (10.2 months, P<0.01) [18].

Metformin Decreases Risk of Pancreatic Malignancy

A systemic review and meta-analysis of 11 studies (6 cohort, 3 case-control, and 2 randomized controlled trials) by Singh *et al*. in 2012 looked at 1,770 cases of pancreatic cancer in 730,664 patients known to have diabetes [19]. This meta-analysis of 9 observational studies showed no significant correlation between metformin use and the subsequent risk of developing pancreatic cancer (adjusted OR=0.76, 95% CI: 0.57-1.03, P=0.073) [19]. Another meta-analysis by Zhang *et al*. [20] of literature published in electronic databases till June 2012 analyzed 37 studies and included 1,535,636 participants with pancreatic, liver, colorectal, breast and prostate cancers. They were able to show that for pancreatic cancer patients, there is a 46% risk reduction among metformin users, with a significant inverse relationship between cancer incidence and metformin use. This meta-analysis showed that metformin can reduce the mortality of overall cancer, liver cancer and breast cancer as well as the incidence of overall cancer, liver cancer, pancreatic cancer, colorectal cancer and breast cancer.

What Have We Learned at the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting?

HbA1c as a Predictive Marker in Pancreatic Cancer (Abstract #4039 [21])

Based on the theory that new-onset diabetes might be a presenting symptom of pancreatic cancer, Fan *et al*. assess the role of using hemoglobin-A1c (HbA1c) as an objective and quantifiable measure of glucose intolerance and in predicting clinical outcomes in pancreatic ductal adenocarcinoma. The data was collected from 656 patients who presented to the Johns Hopkins Pancreas Multidisciplinary Cancer Clinic from 2009 to 2012. HbA1c values were collected prospectively. Univariate Cox regression analyses and multivariable proportional hazards models were used to identify poor prognostic factors for overall survival. They reported higher HbA1c values in patients with malignant disease than patients with benign pancreatic disease (6.1% *vs*. 5.6%, P<0.001).

Interestingly, they also reported through univariate analyses that HbA1c ≥6.5%, age ≥65 years, ECOG ≥1, CA 19-9 >90 U/mL, tumor size >3 cm, and advanced stage are significantly associated with inferior survival (all HR>1, P<0.05) but after multivariate analysis with backward elimination, all of the above factors, except for tumor size >3 cm, remained in the model for inferior survival.

This study demonstrates that HbA1c level at cancer presentation correlates with stage of the disease and predicts survival among all stages of pancreatic ductal adenocarcinoma and highlights the utility of HbA1c as a potential screening tool and prognostic factor.

Benefit of Metformin in Pancreatic Cancer Patients with Diabetes (Abstract #e15110 [22])

Esbah *et al*. performed a retrospective analysis of 467 patients diagnosed with pancreatic cancer from 2003 to 2012. Median age was 60 years (range: 20-85 years) and median tumor size was 42 mm (range: 14-145 mm). Twenty-three patients had stage 1 (4.9%), ninety-seven patients stage 2 (20.8%), seventy patients stage 3 (15.0%) and two-hundred seventy-seven patients had stage 4 disease (59.3%) according to the 2012 TNM staging system. Diabetes mellitus was detected in 173 (37.0%) patients, of which 98 patients had stage 4 disease (56.6%). This study showed that in stage 3 pancreatic cancer patients with diabetes mellitus, the median overall survival was 16 months in metformin users and 10 months in non-metformin users (P=0.02). They were also able to demonstrate a superior median overall survival of diabetic pancreas cancer patients as compared to non-diabetics.

The Impact of Diabetes Mellitus and Metformin on Survival of Patients with Advanced Pancreatic Cancer Receiving Chemotherapy (Abstract #4044 [23])

Oh *et al*. were interested in the impact of diabetes mellitus in patients with advanced pancreatic cancer who receive palliative chemotherapy. The study enrolled 349 patients with advanced pancreatic cancer between 2003 and 2010, and patients were stratified in accordance with 2010 diabetes mellitus criteria (AHA/ADA). A two-year cut-off was used to define remote-onset *vs*. recent-onset diabetes mellitus. One-hundred eighty-three (52.4%) patients with advanced pancreatic cancer had diabetes mellitus. Among those who had diabetes mellitus, 160 had diabetes mellitus at the

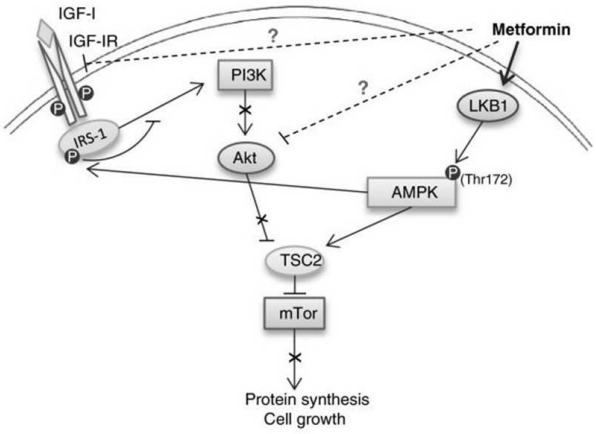

Figure 1. Metformin activates AMPKThr172 through the LKB1 signalling pathway. Activated AMPK inhibits cell growth by repressing mTOR activity through activation of TSC2 and phosphorylation of inhibitory serine residues on IRS-1. In addition, metformin suppresses IGF-IR activation and reduces IRS-1 levels, which disable further signalling through the PI3K/Akt pathway (from Karnevi *et al.* [26], with permission).

time cancer was diagnosed and the remaining 23 developed diabetes mellitus during the course of advanced pancreatic cancer treatment. By the end of treatment, 73.2% of diabetes mellitus patients received antidiabetic medications that were either metformin (n=56), sulfonylurea (n=62), or insulin (n=43). This study showed through multivariate analysis that the diagnosis of diabetes (HR=0.788; P=0.05) conferred a positive effect on overall survival (8.4 months in diabetes mellitus patients *vs*. 7.5 months in non-diabetes mellitus patients; P=0.04), whereas both cancer extent (HR=1.792; P<0.001) and weight loss during chemotherapy (HR=1.270; P=0.08) were associated with diminished overall survival. In a subgroup analysis among diabetes mellitus patients, recent-onset diabetes mellitus conferred prolonged overall survival, compared with remote onset/subsequent diabetes mellitus (9.8 *vs*. 7.9 months, respectively; HR=0.789; P=0.142). They we also able to show that, metformin recipients survived longer (HR=0.693; 95% CI: 0.492-0.977; P=0.036).

Discussion

Given its poor prognosis and high incidence, identifying individuals at high risk for pancreatic cancer and modifying those risk factors would serve as important tools for early detection and treatment of pancreatic cancer. Several attempts are made to identify an effective screening and prognostic tool for pancreatic cancer. The above studies demonstrate that recent-onset diabetes mellitus within two years of diagnosis and metformin treatment are positive prognosticators and are associated with prolonged overall survival. Abstract #4039 showed that not only the presence of diabetes but also the level of HbA1c at the time of diagnosis correlates with disease stage and predicts survival among all stages of pancreatic cancer patients. Therefore, this standard test could emerge as a cheap and reliable screening tool and prognostic factor in pancreatic cancer that can be used alone or in conjunction with other parameters.

Several mechanisms have been suggested through which metformin can indirectly modify cancer risk. This lead metformin to attract attention as being a novel anti-cancer agent. One proposed mechanism though which metformin can decrease cancer risk is by reducing insulin resistance associated hyperglycemia and hyperinsulinemia mainly by affecting the insulin-IGF1 signaling cascade [24, 25]. Recently, Karnevi *et al*. showed that there are direct anti-tumor activities of pancreatic cancer cell lines involving $AMPK^{Thr172}$ activation and suppression of the insulin-IGF signalling pathways (Figure 1) [26].

These *in vivo* studies are translated clinically in studies similar to that presented in Abstracts #4044 and #e15110 showing that metformin treatment serves as a positive prognosticator, especially in patients with diabetes mellitus diagnosed within 2 years of pancreatic cancer and in stage 3 pancreatic cancer patients with diabetes mellitus. With these data, we have a better understanding that the diagnosis of diabetes or insulin resistance is surrogate to an early marker of pancreatic dysfunction and carcinogenesis, and that metformin or other anti-diabetic medications that interfere with this process, might serve as a valuable anti-tumor agent in conjunction with other well established therapies for this aggressive disease. Table 1 summarizes few of the ongoing studies testing metformin in pancreatic cancer.

Conflicts of interest The authors have no potential conflicts of interest

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Table 1. Ongoing clinical trials assessing the role of metformin in pancreatic cancer.

	Phase	Type	Age (years)
Metformin Plus Modified FOLFOX 6 in Metastatic Pancreatic Cancer	II	Biomarker/laboratory analysis, treatment	18 and over
Combination Chemotherapy with or without Metformin Hydrochloride in Treating Patients with Metastatic Pancreatic Cancer	II	Treatment	18-75
Metformin Combined with Chemotherapy for Pancreatic Cancer	II	Treatment	18-80

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