Metformin Use May Not Improve Pancreatic Cancer Survival

PHILADELPHIA — Metformin use did not improve survival of patients with pancreatic ductal adenocarcinoma (PDAC) in a retrospective cohort study, according to data presented here at the AACR Annual Meeting 2015, April 18-22.

“The diabetes drug metformin is being used in some cancer treatment trials based on epidemiologic studies that have reported that use of metformin reduces the risk of death from cancer,” said Roongruedee Chaiteerakij, MD, PhD, of the Division of Gastroenterology and Hepatology at Mayo Clinic Cancer Center in Rochester, Minnesota. “This study highlights the importance of appropriate design of retrospective studies and the necessity of conducting prospective studies with solid rationale for determining the effect of diabetes drugs on cancer risk or death.”

According to Chaiteerakij, several epidemiological studies based on retrospective data have reported that metformin is associated with longer survival from different cancers, including pancreatic cancer. Cancer clinical trials have been opened that incorporate metformin in a treatment arm, in part based on these studies, but whether metformin has a beneficial effect on improving survival of cancer patients remains unproven.

In this retrospective study to comprehensively assess metformin use and survival, Chaiteerakij and colleagues used data from 1,360 patients with PDAC who had data available from the Mayo Clinic Specialized Programs of Research Excellence (SPORE) in pancreatic cancer database. Patients were categorized by metformin use into five groups depending on when they used metformin, from those who had never used metformin to those who started taking metformin more than 30 days after PDAC diagnosis.

The median survival for patients who did not use metformin was 308 days, compared with 292 days for patients with various metformin exposures, which was not statistically different. The longest survival, for 818 days, occurred in patients who started taking metformin more than 30 days after PDAC diagnosis.
“These patients already survived more than 30 days, suggesting that there is an inherent survival bias in this group of patients,” Chaiteerakij said. “After accounting for these unintended biases, the benefit of metformin was not confirmed in our study.”

When the researchers looked at only the 413 patients in the study with resectable disease, they did find a trend toward improved survival among metformin users, but it was not statistically significant.

“Studies of medication exposure and cancer survival warrant very careful and detailed data collection, which is not always possible in a retrospective study design,” Chaiteerakij said. “Researchers should exercise caution when initiating clinical trials based on retrospective epidemiologic studies.”

This study was supported in part by the National Cancer Institute SPORE research grant. Chaiteerakij declares no conflicts of interest.


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Abstract Number: 8687

Title: Metformin use does not increase survival of pancreatic cancer patients: A Cautionary Lesson

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Abstract Body:

Background: Epidemiologic studies have suggested that metformin use is associated with cancer death reduction. The results for pancreatic ductal adenocarcinoma (PDAC) are inconsistent. Retrospective studies of cancer survival may potentially have unintended biases; due to complexities of diabetes management, metformin use exposure is commonly categorized as simply "yes/no." Nevertheless, in part based on epidemiologic studies, there are at least 20 open cancer clinical trials that include metformin in a treatment arm. We aimed to study metformin use and survival of patients with PDAC, addressing potential inherent biases.

Methods: A retrospective cohort study for the years 2000-2011 was conducted using the patient database of the Mayo Clinic Specialized Programs of Research Excellence (SPORE) in Pancreatic Cancer. 1,360 PDAC patients (59% male; mean age 67) with diabetes were studied; overall survival was the primary outcome. Initiation and duration of metformin use was carefully abstracted from medical records. Patients were categorized into 5 groups based on metformin initiation: (A) Never used, n=908 (reference group); (B) Metformin started >1 year prior to PDAC diagnosis, n=84; (C) Metformin started within 1 year prior to PDAC diagnosis, n=212; (D) Metformin started <30 days post-PDAC diagnosis, n=104; (E) Metformin started >30 days post PDAC diagnosis, n=34. Hazard ratios (HR) and 95% confidence intervals (C.I.) for survival differences between groups were computed using Cox proportional hazards models, adjusting for age, sex, disease stage, body mass index, and diagnosis year group.

Results: Median survival of patients in Groups B-E was 292 days compared to 308 for Group A; this was not significantly different. However, among 413 resectable patients, metformin users appeared to survive longer than non-users (782 vs. 612 days, p=0.07). Survival in each group was 308, 245, 249, 243 and 818 days, respectively. Because Group E had already survived >30 days, a bias existed. With Group E excluded, there was no survival difference among the other 4 groups (p=0.18). Compared to Group A, HR and 95% C.I. for metformin use were 1.08 (0.85-1.37), 0.99 (0.85-1.17), 1.04 (0.83-1.31) and 0.49 (0.33-0.74), for Group B-E, respectively.

Conclusions: Our thorough analysis suggests that metformin use does not improve survival of patients with PDAC. The benefit of metformin was observed only in patients who started metformin post-PDAC diagnosis; however, there is an inherent survival bias in this group of patients. Studies of medication exposure and cancer survival warrant very careful and detailed data collection. Researchers should exercise caution when initiating clinical trials based on retrospective epidemiologic studies.