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Title of the Project:

Prophylactic Use of Antihistamines to Reduce Dermatological Adverse Events of Immune Checkpoint Inhibitors

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Investigators: Adam Bailey, Lisa Davis

ABSTRACT

Specific Aims: To determine if there are any differences in rate or severity of dermatological AEs in patients that are taking antihistamines prior to starting therapy versus patients that are not.

Methods: Patients that will be included in this study will based on anonymized data we have received from drug manufactures. A data sharing request form to Bristol Myers Squibb and Merck was submitted.

Main results (from a separate research problem) In pancreatic cancer, diabetic patients were diagnosed with stage IV cancer less often non-diabetic patients, (43.5% vs 51.1%, p=0.049) and more often with stage II (30.1% vs 21.3% p=.006).

Conclusions: Patients with a history of diabetes did not have higher rates of advance staged pancreatic cancer. Further research exploring the relationship between impaired glucose control and pancreatic cancers needs to be done.

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INTRODUCTION

Immunotherapy is a relatively new and rapidly growing field in the oncology world. Certain cancer cells have the ability to evade the host's natural defense system by targeting specific checkpoints and stopping the immune response[1]. However, the discovery of immune checkpoint inhibitors (ICI) has allowed us to block this resistance mechanism of some cancers to more effectively treat patients. In 2011 the first ICI, ipilimumab, was approved, and since then there are now a total of eight on the market.

A downside of using ICI to increase the activity of the immune system, is the immune-related adverse events (AEs) that can come with treatment. These AEs can have a wide range of potential toxicities, ranging from something as minor as a grade 1 pruritus to severe as a grade 5 pneumonitis. Unfortunately, the exact mechanisms of these AE's are poorly understood, making it difficult to predict and prevent these outcomes.

Dermatologic AEs are the most common form of these immune-related adverse events and consist mainly of rash, vitiligo, and pruritus. Many of the recommendations to treat grade 1 and grade 2 AE's include the use of a topical steroid with the possible addition of an oral antihistamine[2].

The purpose of this study will be to explore the use of antihistamines to reduce the incidence and/or severity of these AE's. Oral antihistamines are a relatively safe

medication for individuals, and if shown effective, could be a simple way to lessen these common problems in patients.

METHODS

Design: A retrospective cohort design will be used for this study.

Subjects: Patients that will be included in this study will based on anonymized data we have received from drug manufactures. We will be submitting a data sharing request form to Bristol Myers Squibb and Merck.

Data Collection: Data will be collected directly from the manufacturers of the ICI. We will submit a data sharing request form to Bristol Myers Squibb and Merck per their protocol with hope that after they are reviewed, we will receive the specific anonymized data sets we are inquiring about.

The data collection forms used will contain no protected health information (PHI) and will be stored on a secure server at the University of Arizona College of Pharmacy which is only accessible to the investigators of the project.

Data Analysis: Patients will be divided into groups depending if they are taking antihistamines or not. A determination will be made if they have experienced a dermatologic AE from therapy. Frequencies and percentages for each group will be calculated and group will be compared using a Chi Square test

RESULTS (from a separate research problem)

Data from a total of 1317 patients from The Hospital of the University of Pennsylvania was collected for this study. Inclusion criteria was a diagnosis of pancreatic

adenocarcinoma, that was histologically confirmed, and previously untreated. Patients were put into the diabetes mellitus (DM) group if they had a history or diagnosis of long-term diabetes, with at least 1 HgA1c value. The definition of diabetes is based on the guidelines set by the American Diabetes Association in January 2015. These guidelines define diabetes as fitting one of four criteria: A1c $\geq$ 6.5%, FBG $\geq$ 126 mg/dL, 2-hr BG $\geq$ 200 mg/dL drink oral glucose tolerance test, and random BG $\geq$ 200 mg/dL.

Of the 320 DM patients and 1090 non-diabetic patients that were included, 34 and 188 patients respectively did not have their cancer clinical stage recorded. Table 1 shows the portion of patients and what cancer stage they were diagnosed in. There was a statistically significant decrease in stage IV patients in the DM vs non-DM group, (43.5% vs 51.1%, p=0.049) and a statistically significant increase in stage II patients in the DM group vs non-DM group (30.1% vs 21.3%, p=0.006). There were no statistical differences in stage I or III.

Table 1.

	Diabetes Group (n)	**Non-Diabetes Group (n)**	**p-value**
Stage I	**15.8% (33)**	**16.0% (144)**	**0.6**
Stage II	**30.1% (63)**	**21.3% (192)**	**0.006**
Stage III	**10.5% (22)**	**11.6% (105)**	**0.07**
Stage IV	**43.5% (91)**	**51.1% (461)**	**0.049**

DISCUSSION (from a separate research problem)

The hypothesis that we would see higher staged cancers in DM was not shown, and interestingly the opposite outcome was shown. Given the many possible confounding factors that are be present, it's hard to surmise what this finding represents. For example, one hypothetical explanation is that diabetic patients might be seeing health care providers more often, which could increase the chances of catching a pancreatic cancer diagnosis at an earlier stage.

It is also important to keep in mind that this data is purely a proportion of what stage of cancer the patient has at diagnosis, not overall risk of pancreatic cancer. For example, it is possible that a DM patient is twice as likely to be diagnosed with pancreatic cancer, but for some other reasons it is diagnosed at an earlier stage.

Another factor that should be considered is if there is any relationship between DM medications and the role they play in malignancies. Metformin is first line in DM management, and has shown some potential anti-neoplastic effects in pancreatic cancer. Further research needs to be done to explore this relationship.

There are two unique ways that pancreatic cancer is staged. The more general TNM staging that this study used is applied to a wide range of cancers. Tumor size, lymph node involvement, and whether it has metastasized are taken into account to classify the cancer as stage I, II, III, or IV.

The second method used is to classify the cancer as whether it can be removed by surgery and where it has spread. The stages in this system are resectable, borderline resectable, locally advanced, and metastatic. This method is a more common

way to classify pancreatic cancer because with TNM staging, doctors often will classify the tumor size during surgery, but many of these patients do not ever receive surgery. Because this is a more treatment focuses staging methodology, further studies done may consider using that information if available to improve generalizability.

CONCLUSIONS

In this study, patients with a history of diabetes did not have higher rates of advance staged pancreatic cancer. Further research exploring the relationship between diabetes mellitus and pancreatic cancers needs to be done.

VIII: REFERENCES

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