A Link Between Lorazepam & Worse Outcomes in Pancreatic Cancer

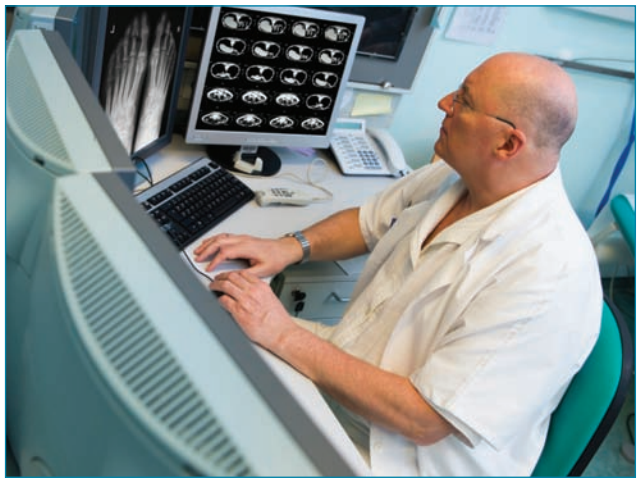
BY CATLIN NALLEY

A team of researchers found that the use of lorazepam was associated with a shorter progression-free survival among patients with pancreatic cancer when compared with patients who did not receive this drug. These findings underscore the need for further research to better understand the impact of lorazepam and other similar agents on cancer outcomes (*Clin Cancer Res* 2023; https://doi.org/10.1158/1078-0432.CCR-23-0547).

While benzodiazepines like lorazepam are often prescribed to patients to help relieve symptoms such as anxiety and insomnia associated with cancer treatment, the effect of these drugs on cancer outcomes has not been thoroughly explored, according to senior study author Michael Feigin, PhD, Associate Professor of Oncology in the Department of Pharmacology and Therapeutics at Roswell Park Comprehensive Cancer Center.

"When we study response to therapy, we think of treatments like chemotherapy or immunotherapy, but patients are also given a lot of medicines for anxiety and pain," Feigin noted. "We wanted to understand the impact of some of these palliative care drugs on the tumor."

With this in mind, Feigin and colleagues initiated a study to gain further insight into the connection between benzodiazepines and survival outcomes in cancer patients, as well as the pancreatic cancer tumor microenvironment and cancer-associated fibroblast signaling.



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Study Design

This multi-faceted research effort used multivariate Cox regression modeling to retrospectively measure associations between Roswell Park cancer patient survival outcomes and benzodiazepine prescription records. The study authors first examined how many patients take benzodiazepines during their cancer treatments. They used a web-based tool at Roswell Park to analyze clinical data. Benzodiazepine prescription records (i.e., alprazolam, lorazepam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, oxazepam, temazepam, and triazolam) among patients were compared.

The study population included primary cancers of the prostate, pancreas, ovary, kidney, head and neck, corpus uteri, colon, breast, brain, and invasive nevi/melanomas. The study authors noted that patients with multiple primary cancers were excluded from this analysis.

Feigin and his team went on to examine the relationship between benzodiazepine use and survival in pancreatic cancer patients. Survival outcomes of Roswell Park patients who received chemotherapy between 2004 and 2020 were assessed.

"To account for potential imbalances in patient demographic and clinical characteristics, multivariable Cox regression models were used to evaluate the association between groups (i.e., benzodiazepine usage) and the survival outcomes while adjusting for age, sex, race, clinical stage, additional treatments, and progressive disease [for overall survival and disease-specific survival only]," the researchers explained.

In this study, Feigin and colleagues evaluated the impact of lorazepam on the murine pancreatic ductal adenocarcinoma (PDAC) tumor microenvironment via immunohistochemistry chemistry, H&E, Masson's trichrome, RNAscope, and RNA sequencing.

"ELISA and qPCR were used to determine the impact of benzodiazepines on IL6 expression or secretion by human-immortalized pancreatic cancer-associated fibroblasts," they outlined. "PRESTO-Tango assays, reanalysis of PDAC single-cell sequencing/TCGA datasets, and GPR68 CRISPRi knockdown cancer-associated fibroblasts were used to determine the impact of benzodiazepines on GPR68 signaling."

> "This research supports the need for prospective clinical trials to determine how different benzodiazepines impact survival not only in pancreatic cancer, but also other malignancies."
>
> *—Michael Feigin, PhD, at Roswell Park Comprehensive Cancer Center*

Takeaways & Next Steps

When examining benzodiazepine prescription data in all cancer types, the study authors found that 30.9 percent of patients had received benzodiazepines. The highest rate of benzodiazepine use was observed among patients with pancreatic cancer (40.6%). Compared to their male counterparts, females had an equal or higher record of benzodiazepine prescriptions (34.2% vs. 27.4%) across all cancers.

Given the high frequency of benzodiazepine use among pancreatic cancer patients, Feigin and colleagues took a closer look at how it correlated with survival outcomes in this patient population. Their initial investigation showed no significant difference in progression-free survival. However, benzodiazepines were associated with significantly improved disease-specific survival compared to those without benzodiazepine prescription records.

"Improved disease-specific survival can be partially attributed to imbalances in patient demographic and clinical characteristics," Feigin noted. "Patients prescribed benzodiazepines were significantly more likely to be White, younger, and less likely to receive radiotherapy or surgery compared with non-benzodiazepine users."

To address this, covariate-adjusted analyses to account for age, sex, race, clinical stage, additional treatments, and progressive disease were conducted. When they adjusted for these factors, any benzodiazepine use was associated with a 30 percent lower risk of pancreatic cancer-related death, according to the researchers.

"The most commonly prescribed benzodiazepine in pancreatic cancer, and all other cancer types with the exception of brain cancer, was midazolam, a short-acting agent (half-life 2-5 hours) often used as a sedative prior to surgery or medical procedures," noted Feigin and colleagues.

Lorazepam (40 patients) and alprazolam (27 patients)—both intermediate-acting drugs with a half-life of 6-24 hours—were the second and third most commonly prescribed benzodiazepines in pancreatic cancer patients, respectively. These agents are often given to patients for the treatment of anxiety and anticipatory nausea prior to chemotherapy.

Further investigation of the link between specific benzodiazepines and pancreatic cancer survival outcomes demonstrated that lorazepam was associated with significantly worse progression-free survival when compared to individuals who were not prescribed this agent. Feigin reported that patients who received lorazepam had a 3.83-fold higher risk of disease progression or death versus patients who did not (29 patients).

Conversely, prescription of alprazolam was correlated with a significant improvement in progression-free survival. The study authors observed a 62 percent lower risk of disease progression or death among pancreatic patients who received alprazolam when compared with their counterparts who did not take this particular benzodiazepine (42 patients).

The differences in patient outcomes between lorazepam (40 patients) and alprazolam were surprising, according to Feigin. "These benzodiazepines are very similar with some small structural differences," he told *Oncology Times*. "So we really wanted to understand why lorazepam was associated with this poor outcome."

In mouse models of pancreatic cancer, the researchers saw significant changes in the tumor microenvironment with lorazepam. In particular, the deposition of collagen was increased in the tumors of the mice treated with this drug, said Feigin, noting that the blood vessels were constricted. "These are all things that were known to be associated with resistance to chemotherapy."

First author of the study, Abigail Cornwell, a graduate student in Feigin's lab, spearheaded mechanistic studies that revealed that lorazepam may activate GPR68—a protein that is highly expressed on fibroblasts that support the tumor.

"GPR68 boosts expression of the cytokine IL-6, which is a pro-inflammatory molecule in the pancreatic tumor microenvironment, that can lead to increased tumor growth," explained Feigin, while noting that alprazolam has the opposite effect as lorazepam. "It has potently decreased IL-6, and we think this decreases the inflammatory potential of these tumors. These findings suggest that the difference between the epidemiology was possibly explained by activation of GPR68 in fibroblasts."

However, Feigin cautioned it is too soon to say patients should stop taking one drug or start taking another. "There is more to learn about the clinical implications of these findings and additional research is needed."

Feigin and colleagues took their research a step further and evaluated the connection between lorazepam and alprazolam usage and patient outcomes among other cancer types. The researchers compared survival outcomes in Roswell Park patients with primary cancers of the brain, breast, corpus uteri, head and neck, skin, kidney, ovary, colon, and prostate. "We found that lorazepam in general was associated with a worse outcome across many different tumor types—some pretty dramatically like melanoma," Feigin said.

Lorazepam was associated with significantly worse overall survival and progression-free survival in prostate cancer, ovarian cancer, invasive nevi/melanoma, head and neck cancer, colon cancer, uterine cancer, and breast cancer when compared to patients who were not prescribed benzodiazepine, according to the study authors.

"In contrast, alprazolam was infrequently associated with significant differences in survival outcomes, with the exception of hormonal cancers where there was significantly worse overall survival and progression-free survival in breast cancer, worse overall survival in prostate cancer, and worse progression-free survival in uterine cancer patients," Feigin and colleagues reported.

"Intriguingly, lorazepam was associated with significantly improved overall survival in patients with brain cancer," they added. "Lorazepam and alprazolam did not correlate with altered survival outcomes in kidney cancer."

Feigin and colleagues acknowledged their research has a number of limitations that must be considered before making any clinical recommendations about the use of benzodiazepines in cancer patients.

"Although our benzodiazepine dosing strategies in vivo were designed based on previous benzodiazepine studies to assess anxiety in mice, the treatment regimen does not completely replicate benzodiazepine use in humans due to differences in drug formulation, drug metabolism, and differences in route of administration," the study authors explained, while also noting benzodiazepine dosage varies based on the indication of use, which was not accounted for in this research.

Additionally, Feigin noted that some of the mouse experiments were "performed on subcutaneously implanted tumors, which have a different microenvironment than tumors that develop in the pancreas."

When asked what comes next, Feigin emphasized the need for further investigation. "Our next steps are really to try and understand what is happening in human patients that are taking these drugs. Do we see the same changes in the tumor microenvironment we observed in mouse models? This research supports the need for prospective clinical trials to determine how different benzodiazepines impact survival not only in pancreatic cancer but also other malignancies." OT

Catlin Nalley is a contributing writer.

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to

1. Explain initial study findings demonstrating a relationship between benzodiazepines and survival outcomes in cancer patients and summarize their implications for clinical practice and research.
2. Identify the associated issues related to pancreatic cancer tumor microenvironment and cancer-associated fibroblast signaling.

Disclosure: All authors, faculty, staff, and planners have no relevant financial relationships with any ineligible organizations regarding this educational activity.