Metformin Exposure and Survival in Glioblastoma: A Large Population Study

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Introduction

- Glioblastoma multiform (GBM) is a primary malignant brain neoplasia occurring in the intracranial tissue/glial cell with a poor prognosis[1]
- Metformin, a first-line therapy for diabetes, is also being investigated for its potential anticancer effects. While several observational studies have examined the association between metformin use and cancer outcomes, the findings have been inconsistent[2,3,4]
- This large population-based study aimed to evaluate the relationship between metformin exposure following GBM diagnosis and all-cause mortality

Methods

Study Design

- This was a retrospective cohort study utilizing the Surveillance, Epidemiology, and End Results (SEER) national cancer registry database linked with Medicare data

Study Population

- Adult patients aged 66 years or older with a diagnosis of GBM between January 1, 2008, and December 31, 2018, were retrieved. The GBM diagnosis was identified using ICD-0-3 code: meninges (C70.0 - 70.9), brain (C71.0-71.9), or central nervous system (C72.0-72.9) and considered the index date
- Patients were included in the study if they had at least 12 months continuous coverage of Medicare Part A and Part B prior to GBM diagnosis and enrollment of Medicare Part D at or before diagnosis. Patients diagnosed on autopsy or by death certificate were excluded from the analysis.
- Patient characteristics, comorbidities, and exposures were assessed during a 1-year baseline period

Metformin Exposure

- Metformin exposure was tracked as a time-dependent covariate. In 30-day intervals during the post-index period, patient records were observed for metformin prescriptions
- Once a patient received a metformin prescription, they were classified as exposed from the beginning of the next 30-day interval onward for the duration of their follow-up

Statistical Analysis

- Time-dependent, covariate-adjusted mortality hazard ratios (HRs) for time-dependent metformin exposure were estimated using Cox regression models

Results

- 16,069 patients with GBM diagnosis were identified
- The average age was 75.3 years, preponderantly male (52.1%) and white (91.1%). 29.1% had diabetes and 13.6% used metformin within a year prior to GBM diagnosis (Table 1)

Table 1. Patient characteristics at GBM diagnosis (n=16,069)

Age, mean (SD)	75.3 (6.6)
Sex	
Male	52.1%
Race	
White	91.1%
Black	4.9%
Hispanic	9.9%
Asian/Pacific Islander	3.7%
Year of GBM diagnosis	
2007-2010	19.1%
2011-2013	23.4%
2014-2016	29.5%
2017-2018	22.4%
Comorbidities	
CCI, mean (SD)	2.0 (2.0)
0	29.2%
1-2	38.9%
3-4	20.6%
≥5	11.2%
Diabetes	29.2%
Cardiovascular disease	32.5%
Obesity	20.9%
COPD	20.3%
Treatment after GBM diagnosis	
Surgery	49.6%
Radiation	15.9%
Chemotherapy	4.8%
Radiation and chemotherapy	38.5%
No radiation or chemotherapy	40.7%
Drug exposure in year prior to GBM diagnosis	
NSAIDs	10.4%
Beta-blockers	35.5%
ACE inhibitors	27.9%
ARBs	17.3%
Statins	42.1%
Insulin	14.4%
Fluoxetine	2.9%
Metformin	13.6%
Other oral diabetes medications	12.1%
All-cause mortality	
Within 3 months of GBM diagnosis	32.6%
Within 6 month of GBM diagnosis	55.8%
Within 1 year of GBM diagnosis	76.1%

Results

- Exposure to metformin after GBM diagnosis had a time-varying association with mortality hazard (Table 2).
- Though not significantly associated with mortality within the first three months of survival, metformin exposure became associated with approximately 20% greater mortality hazard later in follow-up.

Table 2. Hazard ratios for the time-dependent metformin association with survival of entire SEER-Medicare cohort with GBM diagnosis (n=16,069)

Timeframe of Exposure with respect to GBM Dx	Hazard Ratio (95% CI)	*P* Value
Metformin year before	0.92 (0.83-1.01)	0.073
Metformin <3 months	1.02 (0.91-1.14)	0.805
Metformin 3-9 months	1.22 (1.10-1.34)	<.0001
Metformin 9+ months	1.20 (1.09-1.32)	<.0001

Limitations

- SEER-Medicare lacks key clinical details influencing treatment decisions, posing challenges—especially in elderly populations
- Confounding by indication remains a concern since metformin users tend to be different from others in ways related to survival for which we could not control, including differences from those taking other forms of anti-hyperglycemic such as the stage of diabetes and clinical characteristics.

Conclusions

- This large population-based study found little evidence of survival benefits associated with metformin exposure after GBM diagnosis
- Further clinical trials are needed to clarify the potential impact of metformin on GBM survival outcomes

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