Would Exposure to Metformin Reduce Mortality in Patients with Glioblastoma?

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Introduction

- Glioblastoma multiform (GBM) is a primary malignant brain neoplasia occurring in the intracranial tissue/glial cell.
- The annual incidence of GBM is 3.19 cases per 100,000 people in the United States and can be extremely infiltrative and causes rapid onset of symptoms, often only weeks before diagnosis.
- Despite aggressive treatments, such as surgery combined with radiation and chemotherapy, median survival among GBM tumor patients remains poor, between 12 to 15 months.
- Metformin, a first-line therapy for treating diabetes, it is increasingly being used for its anticancer effects; these anti-tumor effects are hypothesized to be mediated through insulin receptor/insulin-like growth factor receptor-1 signaling and moderation of cellular effects of hyperglycemia and hyperinsulinemia. However, the literature is limited on the effect of metformin dose on overall survival in patients with GBM.

Objectives

- To investigate exposure to metformin and 1-year mortality in patients with GBM.

Methods

Study Design

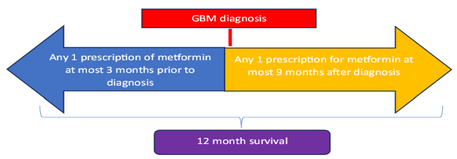
- This was a retrospective cohort study utilizing the Surveillance, Epidemiology, and End Results (SEER) national cancer registry database linked with Medicare data.

Study Population

- Adult patients aged > 66 years or older with a diagnosis of GBM between January 1, 2008, and December 31, 2019, 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 were assessed during a 1-year baseline period

Metformin Exposure

- Patients were identified as exposed to metformin if they have filled at least 1 prescription of metformin between 3 months prior to GBM diagnosis and 9 months after GBM diagnosis (see figure below)



Statistical Analysis

- Descriptive analyses were conducted for all variables of interest.
- A multivariable logistic regression analysis was conducted to determine the association between covariates of GBM patients and 1-year survival.
- The data were analyzed using the SAS® software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Table 1. Characteristics of Glioblastoma Patients According to Metformin Exposure and 1-year Survival in the SEER-Medicare database, 2008-2019. (N=16,116)

	Exposed to metformin[a] (n=2,676)	Not exposed to metformin (n=13,490)	Total (N=16,116)
	16.6%	83.7%	100%
Characteristic			
Age (years), mean (SD)	74.0 (5.8)	75.4 (6.6)	75.2 (6.5)
Age groups			
66-70	35.2%	29.7%	30.7%
71-75	30.9	27.5	28.2
76-80	21.4	23.1	22.9
≥81	15.8	24.2	22.9
Sex, Male	57.8	51.5	52.7
Race			
White	87.7	91.8	91.4
Black	6.8	4.5	4.9
Asian or Pacific Islander	4.9	3.3	3.6
Other/Unknown	0.6	0.5	0.5
Hispanic Ethnicity	16.0	8.6	9.9
Year of diagnosis			
2008-2010	15.4	18.5	18.0
2011-2013	22.3	22.0	22.1
2014-2016	26.8	28.1	27.9
2017-2019	35.5	31.5	32.2
CCI, mean (SD)	2.8 (2.0)	2.0 (2.0)	2.1 (2.0)
0	6.9	27.9	24.5
1-2	44.2	40.4	41.2
3-4	30.2	20.6	22.2
≥5	18.7	11.1	12.4
Top CCI component			
Acute MI	2.5	2.4	2.5
Cardiovascular Disease	34.5	34.4	34.5
Congestive heart failure	14.0	12.5	12.8
COPD	19.2	22.1	21.7
Dementia	5.2	5.9	5.8
Diabetes	29.9	6.2	10.2
History of MI	7.1	5.7	5.9
Liver disease	6.9	5.8	6.0
Paralysis	15.0	14.7	14.8
Peripheral Vascular Disease	17.3	16.9	17.0
Renal disease	13.6	13.9	13.9
Rheumatoid arthritis	3.0	4.2	4.0
Obesity	35.3	22.0	24.3
Cancer therapy			
Radiation	55.4	53.1	53.6
Surgery	51.9	51.2	51.5
Chemotherapy	45.6	43.1	43.6
Drug exposures			
NSAIDs	19.8	15.7	16.4
Beta-blockers	49.2	40.4	42.0
ACE inhibitors	47.9	30.5	33.5
ARBs	29.6	20.1	21.8
Statins	72.3	50.0	53.8
Insulin	41.2	9.7	15.0
Other oral diabetes medications[b]	49.4	6.8	18.2
Fluoxetine	3.6	3.2	3.3
Death			
Within 1 year from diagnosis	73.0	72.2	72.6

- A total of 16,116 patients (mean age, 75.2 and 52.7% male) were diagnosed with GBM between 2008 and 2019. Of these, 17% (n=2,676) patients were exposed to metformin (Table 1).
- Patients exposed to metformin tended to be male, younger, black, Hispanic, and with more comorbidities.

References

Results

Table 2. Odds Ratios Assessing the Association between Covariates of Patients 1-year Survival after GBM diagnosis

Covariate	OR (95% CI)
Age (years)	
66-70	Reference
71-75	1.39 (1.26-1.53)
76-80	1.91 (1.72-2.13)
≥81	2.97 (2.61-3.37)
Sex	
Male	Reference
Female	1.01 (0.94-1.09)
Year of diagnosis	
2008-2010	Reference
2011-2013	0.97 (0.85-1.10)
2014-2016	0.85 (0.75-0.96)
2017-2019	0.39 (0.35-0.44)
Race	
White	Reference
Asian	0.82 (0.67-1.01)
Black	0.84 (0.70-1.01)
Other/Unknown	0.54 (0.31-0.92)
CCI (score)	1.13 (1.11-1.16)
Obesity	1.10 (1.00-1.21)
Cancer therapy	
Radiation	0.63 (0.57-0.69)
Surgery	0.98 (0.90-1.07)
Chemotherapy	0.25 (0.23-0.27)
Drug exposure	
Metformin	0.99 (0.87-1.11)
NSAIDs	0.80 (0.72-0.89)
Beta-blockers	1.08 (0.99-1.17)
ACE inhibitors	1.03 (0.94-1.13)
ARBs	0.93 (0.84-1.03)
Statins	0.88 (0.81-0.96)
Insulin	1.47 (1.30-1.68)
Sulfonylureas	1.08 (0.93-1.26)
Meglitinide	1.31 (0.80-2.13)
Thiazolidinediones	0.82 (0.64-1.06)
DPP-4 Inhibitors	0.82 (0.64-1.06)
SGLT2 Inhibitors	1.41 (0.79-2.53)
GLP-1	0.64 (0.42-0.98)
Fluoxetine	1.35 (1.08-1.68)

- Multivariable logistic regression analysis found that metformin exposure was not associated with 1-year survival (OR: 0.99; CI: 0.87-1.11). Of note, patients who underwent radiation and chemotherapy were more likely to survive at 1-year from diagnosis (OR: 0.63; CI 0.57-0.69 and OR: 0.25; CI 0.23-0.27). Patients exposed to NSAIDs (OR: 0.80; CI: 0.72-0.89), and statins (OR: 0.88; CI: 0.81-0.96) were more likely to survive at 1-year from diagnosis (Table 2).

Limitations

- Metformin users tend to be different from those taking other forms of anti-hyperglycemic due to the stage of diabetes and clinical characteristics.
- As per the way metformin exposure was identified, we acknowledge the presence of immortal time bias for individual that were exposed after the GMB diagnosis. However, its potential effect of the analysis may be mitigated since GBM patients have a short survival.

Conclusions

- In this real-world, large study, we observed that GBM patients exposed to metformin had a similar risk of 1-year survival associated with those who were not exposed to metformin.
- A robust time-varying analysis would be advisable to corroborate these results.

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