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Review Article

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Can Mirtazapine Prevent Common Side Effects of Temozolomide and be Tolerated by Newly Diagnosed Glioblastoma Patients? Experience with Two Patients

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Abstract

Patients newly diagnosed with glioblastoma (GBM) often experience psychological depression, which diminishes their quality of life, and correlates with shorter overall-survival times [1]. The first-line chemotherapy treatment for these patients is temozolomide (TMZ), a drug with several significant side effects, including nausea, vomiting, weight loss, and fatigue [2]. Mirtazapine is a Food and Drug Administration (FDA) approved antidepressant that can stimulate appetite and is occasionally used for insomnia. While there are, to date, no data from GBM patients, mirtazapine has shown anti-nausea and anti-vomiting activity in thoracic cancer patients receiving chemotherapy [3]. The potential of mirtazapine to counter the side effects of TMZ makes the use of mirtazapine in GBM patients of substantial clinical interest. Here we present pilot data from two patients who were clinically depressed post-surgery and prescribed mirtazapine before starting TMZ. Assessments of adherence, adverse events attributable to mirtazapine, depression, sleep and appetite disturbance, and frequency/intensity of nausea and vomiting were made at four- and eight-week follow-up exams. Results show good adherence to both mirtazapine and TMZ, recovery from depression, little disturbance of sleep or appetite, and few episodes of nausea or vomiting. No adverse events attributable to mirtazapine were observed. These findings justify a follow-on Phase II study on the potential of mirtazapine to mitigate the side effects of TMZ in newly diagnosed GBM patients.

Introduction

Glioblastoma (GBM, World Health Organization grade IV astrocytoma) is the most common primary brain tumor. GBM is very aggressive, with a case-fatality ratio approaching 100 percent and a median overall survival of less than two years. Improvements in the clinical management of GBM are urgently needed. Currently, first-line therapy for GBM includes maximum safe resection followed by six weeks of concurrent radiation and temozolomide (TMZ) chemotherapy, followed by six to twelve months of adjuvant TMZ [2]. While TMZ unquestionably extends overall survival for GBM patients, the side effects of TMZ can be troublesome and decrease the patient's quality of life.

Newly diagnosed GBM patients are at high risk for depression. A review by Rooney et al., reports estimates of depression prevalence in adult GBM patients ranging from 15% to 39%, depending on the method of assessment [4]. A meta-analysis by Abazari et al., suggests that, between the diagnostic image and confirmatory surgery, at least 30% of high-grade glioma patients are depressed. Research has also shown that depressed glioma patients are more affected by TMZ side effects, such as nausea and vomiting [5], and experience more sleep disturbances than non-depressed patients [6]. Thus, a well-tolerated medication that simultaneously alleviates both depression and sleep disturbances, and the TMZ-induced nausea and vomiting, would fill a substantial need in the management of GBM.

The data presented here are from a single-arm clinical trial that closed to accrual shortly after opening, in response to the COVID-19 pandemic. The trial screened adult, newly diagnosed GBM patients for depression at a time point after their initial diagnostic surgery and before starting the concomitant radiation-TMZ therapy. Before accrual closed, 2 of 18 patients screened positive for depression (11.1%; 95% CI: 2.3% to 31.2%) and were prescribed mirtazapine (15 mg/day) for eight weeks. These two participants were followed for eight weeks by keeping a daily diary and undergoing clinic visit assessments at four and eight weeks during the study.

Methods

Depression and sleep disturbance were assessed in the clinic by Beck's Depression Inventory (BDI) [7] and the Insomnia Severity Index (ISI) [8], respectively, administered at enrollment, 4 weeks, and 8 weeks on study. At the same time points, weight was abstracted from the medical record. Age, height, race/ethnicity, and sex were abstracted from the medical record at enrollment. Adverse events and serious adverse events were assessed by clinical interview during study visits. Standard mechanisms to cope with medical emergencies were in place throughout.

Patients kept a daily diary for the duration of adjuvant TMZ, wherein they recorded taking TMZ and mirtazapine, rated nausea, vomiting, and poor appetite on separate, seven-point Likert scales (1= 'not at all' … 7 = 'a great deal'), and denoted sleep disturbance as Yes/No. Thus, there are two indicators of appetite (objective weight & self-reported diary entries) and two indicators of sleep disturbance (ISI & diary entry, both self-reported). *Statistics:* Data are presented as frequency counts and associated percentages. No formal tests of significance were conducted, due to the limited nature of the sample.

Results

Patient Characteristics at Enrollment: Both patients were male. Patient 003 identified as mixed-race Hispanic, age 30, with a Karnofsky Performance Score (KPS) of 80 and a BDI total score of 32 ('severe depression'). The other patient (010) self-reported as non-Hispanic White, age 28, with a KPS of 90 and a BDI total score of 24 ('moderate depression').

Adherence: Table 1 presents the adherence scores by participant and four-week interval, corresponding to follow-up clinic visits. Adherence information is from the patient's daily pill diary. Patients 003 and 010 were prescribed adjuvant TMZ for 45 and 48 days, respectively. As shown, both participants reported high adherence to both mirtazapine and TMZ (pooled rate = 97.8% (91/93 for each medicine). Patient 003 did not make diary entries on two non-consecutive days, so his adherence might be underestimated.

Depression Trajectory: Table 1 also presents the total score on Beck's Depression Inventory, along with its interpretation, for each participant and assessment time. As shown, both patients were depressed at enrollment, one severely and the other moderately. The patient initially assessed as moderately depressed recovered to '*normal*' at four weeks on study and was again '*normal*' at eight weeks. The patient assessed as severely depressed at enrollment remained severely depressed at four weeks but recovered to '*normal*' after eight weeks on study. While anecdotal, this pattern of results is consistent with a '*dose response*' relation between time on mirtazapine and degree of depression, although no causality may be inferred due to the limited dataset.

Patient Identifier	Study Timepoint (Weeks)	Mirtazepine Compliance (%)	TMZ Compliance (%)	BDI Score	BDI Interpretation
3	Baseline	n/a	n/a	32	Severe Depression
	1 to 4	26/28 days	26/28 days	39	Severe Depression
	5 to 8	17/17 days	17/17 days	6	Normal
10	Baseline	n/a	n/a	24	Moderate Depression
	1 to 4	28/28 days	28/28d	6	Normal
	5 to 8	20/20 days	20/20d	10	Normal
Combined Results		91/93 days, 97.8%	91/93 days, 97.8%		

Table 1: Proportion of Days each Participant Recorded Taking Mirtazapine and TMZ, and Assessment of Degree of Depression, by Participant and Time of Assessment

Frequency and Severity of Nausea and Vomiting: Table 2 presents the frequency and severity of nausea and vomiting by participant and at the four-week follow-up period. Data shown are condensed from the respective seven-point Likert scales of the daily pill diary. As shown, patient 003 made no entries for nausea and vomiting on four days (three of them consecutive) during the first follow-up period. In the earlier period, pooled across participants, over 89.3% (50/56) of the entries for nausea were 'not at all', and two, both from patient 010, were 'moderate' (3.6% (2/56)). In the same period, 92.9% (52/56) of the pooled entries for vomiting were 'not at all', with 4 blank entries from patient 003 accounting for the remainder. In the later follow-up period, all diary entries from both patients were 'not at all' for both nausea and vomiting.

Patient Identifier	Study Timepoint (Weeks)	Self-Reported Severity and Frequency (Days) of Nausea (first number) and Vomiting (second number)				Total Reporting Days
		Not at all	Moderate	A great deal	Left blank	
3	1 to 4	24/24	0/0	0/0	04-Apr	28
	5 to 8	17/17	0/0	0/0	0/0	17
10	1 to 4	26/28	2/0	0/0	0/0	28
	5 to 8	20/20	0/0	0/0	0/0	20

Table 2: Nausea/Vomiting. Number of Daily Reports and Severity of Nausea and/or Vomiting, by Patient and Assessment Time.

Appetite Disturbances, Weight, and Body-Mass Index: Table 3 presents the frequency and severity of appetite disturbances, along with body weight and body-mass index, by participant and time period. Data on frequency and severity are condensed from the seven-point Likert scale of the daily pill diary. Weight is from clinical exams. For the self-reported data, entries in the '*left blank*' column correspond to the two non-consecutive days during which patient 003 made no diary entries. During the first four weeks on study, 94.6% (53/56) of diary entries were in the '*not at all*' category. Patient 010 reported '*moderate*' appetite suppression on one day. In the later time period, all diary entries made by patient 003 were '*not at all*', as were all but three instances of '*moderate*' appetite suppression reported by patient 10. By inspection, no meaningful change in weight, nor consequently, BMI, occurred for either patient while on the study. These data indicate that neither participant experienced significant appetite suppression from TMZ while taking mirtazapine, although no causal relationship can be inferred.

Patient Identifier	Study Timepoint (Weeks)	Self-Reported Severity and Frequency (Days) of Appetite Disturbances				Weight (kg)	BMI Score and Interpretation
		Not at All	Moderate	A Great Deal	Left Blank		
3	Baseline	n/a	n/a	n/a	n/a	77.8	22.7 (Healthy)
	1 to 4	26	0	0	2	75.4	22.0 (Healthy)
	5 to 8	17	0	0	0	75.2	22.0 (Healthy)
10	Baseline	n/a	n/a	n/a	n/a	87.4	29.2 (Overweight)
	1 to 4	27	1	0	0	85.6	28.6 (Overweight)
	5 to 8	17	3	0	0	85.7	28.6 (Overweight)
BMI: 'underweight' < 18.5; '**healthy**' = 18.5 to 24.9; '**overweight**' 25 to 29.9; '**obesity**' 30 to 39.9							

Table 3: Frequency and Severity of Appetite Disturbance, Body Weight, and Body-Mass Index, by Participant and Time Period.

Sleep Disturbance: Table 4 shows the number of days on which participants reported sleep disturbance in the pill diary and their corresponding ISI scores, along with interpretation, by participant and time period. As may be seen, patient 003 showed no indication of sleep disturbance while on study, although no entry was made for two of the days. Consistent with this, the ISI scores for patient 003 were uniformly unremarkable. Patient 010 had an ISI score of 12 at enrollment, which denotes subclinical insomnia, and indicated sleep disturbance on 10 days (35.7% (10/28)) of the first four weeks on study. At both four and eight weeks on study, patient 010's ISI scores were unremarkable. Patient 010 indicated sleep disturbance on only 1 day of the second four-week interval. The pattern of these findings for patient 010 is consistent with a dose-response relation between sleep disturbance and time on mirtazapine, although no causality may be inferred.

Patient Identifier	Self-Reported Sleep Disturbances				Insomnia Severity Index Results		
	Study Time point (Weeks)	Total Pill-Diary Daily Reports (Yes for Insomnia)			Study Time point (Weeks)	ISI Score	Interpretation
		Yes	No	Unrecorded			
3					Enrollment	5	Not clinically significant
	1 to 4	0	26	2	4 weeks	4	Not clinically significant
	5 to 8	0	17	0	8 weeks	5	Not clinically significant
10	baseline	n/a	n/a	n/a	Enrollment	12	Sub-threshold for insomnia
	1 to 4	10	18	0	4 weeks	0	Not clinically significant
	5 to 8	1	19	0	8 weeks	2	Not clinically significant

Table 4: Sleep Disturbances: Number of Occurrences of Sleep Disturbances and Scores on Insomnia Severity Index, by Participant and Time Point.

Discussion

Our main objective was to assess the tolerability of the antidepressant mirtazapine in newly diagnosed GBM patients for two reasons. First, such patients are at risk for clinically significant psychological depression, and therefore, an antidepressant may be indicated. Secondly, well-known secondary effects of mirtazapine could relieve GBM patients of significant side effects of TMZ chemotherapy, which is the standard of care. Perhaps our most significant finding is the absence of adverse events attributable to mirtazapine in our two patients. As expected, both patients recovered from clinically significant depression to normal affect over the course of the study.

Regarding the second aim, we observed no clinically significant degree of the common side effects of TMZ in these two patients. Self-reported adherence to both medications exceeded 97%. Nausea was reported on only two days, both episodes '*moderate*', and no vomiting was reported. Only four episodes of 'moderate' appetite suppression were reported, and weight/BMI were stable over the study period. Patient 010, who was borderline insomniac at enrollment, reported some sleep disturbances during the first four weeks of follow-up, but only one episode subsequently, and both ISI scores assessed while on mirtazapine were normal. The other patient had no trouble with sleep.

Our interpretation is limited by three factors: the observational nature of the study, the small sample size, and the lack of long-term follow-up. We cannot know what role, if any, mirtazapine played in the observed low prevalence of common side effects of TMZ. After the combined radiation and TMZ treatment, GBM patients generally receive maintenance TMZ for approximately 6-12 months; however, the present data do not address this period. Nevertheless, we offer as pilot data two examples of newly diagnosed, clinically depressed GBM patients who tolerated mirtazapine, recovered from depression, and showed little to none of the common side effects of TMZ chemotherapy. These encouraging observations justify a more extensive prospective study of mirtazapine to prevent nausea and vomiting in GBM patients receiving chemotherapy.

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