Real-world treatment patterns and outcomes in US patients newly diagnosed with glioblastoma multiforme by O6-methylguanine DNA methyltransferase promoter status

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Introduction

- Glioblastoma (GBM) is the most aggressive diffuse glioma of astrocytic lineage and is considered a grade IV glioma[1]
- The average annual age-adjusted incidence rate was 6.0 per 100,000 population from 2010 to 2014 in the US, with a 5-year survival rate of approximately 5%[2]
- GBM remains incurable with a median survival of only 15 months[3]
- Current standard therapy tends to include maximal safe surgical resection and concurrent radiation with temozolomide (TMZ), an oral alkylating chemotherapy agent, and then adjuvant chemotherapy with TMZ[4]
- In newly diagnosed GBM, methylation of O6-methylguanine-DNA methyltransferase (MGMT) promoter has been shown to predict response to alkylating agents.[5] Different randomized trials have shown that methylation of the MGMT promoter in GBM patients is significantly associated with higher survival rates if treated with radiotherapy and TMZ[6]

Objectives

- To describe the relationship between MGMT testing, treatment patterns and response of patients with newly-diagnosed GBM in the US
- Analyses presented describe the following groups of patients:
  - Patients that were MGMT-tested and not MGMT-tested
  - Of those that were tested, patients with methylated MGMT promotor status and unmethylated MGMT promotor status

Methods

- A real-world, cross-sectional study using the Adelphi GBM Disease Specific Programme (DSP) was conducted between March and October 2019
- Physician inclusion criteria:
  - Medical oncologist or neuro-oncologist
  - Responsible for treatment decisions for at least 5 GBM patients in a typical month
- Each physician provided patient record forms (PRFs) for the next 8 consecutive consulting GBM patients, of whom 6 were on a 1st line (1L) active drug treatment and 2 were on a 2nd line (2L) or later active drug treatment for their GBM
- Patient inclusion criteria:
  - Confirmed diagnosis of GBM, ≥18 years old, not participating in a clinical trial at time of study and receiving an active drug treatment for their GBM at point of consultation
- Patient demographics, clinical characteristics, treatment patterns and response to treatment were collected via patient record forms (PRFs)
- Bivariate analysis was conducted between subgroups of patients. Statistical comparisons within this analysis do not infer causality and are purely to aid the descriptive nature of this analysis

Results

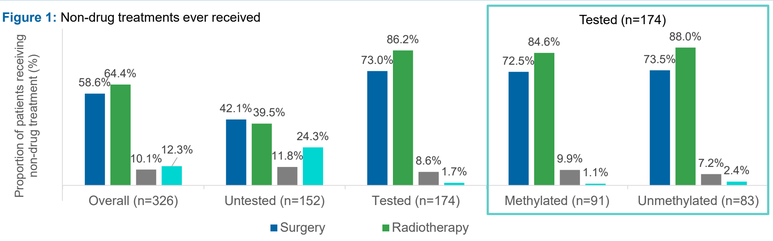
- 40 physicians reported on 326 GBM patients receiving 1L treatment at time of data collection, of whom 65% were male, mean age was 60.3 years, and most patients were located in the Northeast (36%) or South (33%) of the US (Table 1)
- 174 (53%) received MGMT testing, of whom 91 (52%) were MGMT promotor-methylated and 83 (48%) MGMT promotor-unmethylated (Table 1)
- MGMT-tested patients were more likely to be located in Northeast US (48% vs 22%; p=<0.0001), be diagnosed with de novo GBM (92% vs 68%; p=<0.0001), have unifocal GBM (81% vs 57%; p=<0.0001), have a better ECOG score (0-1: 72% vs 51%; p=0.0005) and have a tumor resectable at diagnosis (68% vs 44%; p=<0.0001) vs MGMT-untested patients (Table 2)
- MGMT promotor-methylated patients had a longer time since diagnosis (19.5 vs 13.2 weeks; p=0.0156) and had a tumor that was more likely to be resectable at diagnosis (76% vs 59%; p=0.0202) than MGMT promotor-unmethylated patients (Table 2)
- Overall, 59% of patients received surgery, 77% received temozolomide (TMZ), 64% radiotherapy, and 10% tumor-treating fields (Figure 1 and 2)
- MGMT-tested patients were more likely to receive surgery (73% vs 42%; p=<0.0001) and TMZ (95% vs 56%; p=<0.0001) but less likely to receive bevacizumab (5% vs 20%; p=<0.0001) and Carmustine (3% vs 11%; p=0.006) than MGMT-untested patients. At time of data collection there were no differences between duration on 1L for MGMT-tested and MGMT-untested patients (10.9 vs 12.9 weeks; p=0.3035) (Figure 2)
- MGMT-tested patients were also more likely to receive radiotherapy concurrently with 1L treatment (86% vs 40%; p=<0.0001) (Figure 1), of which they received fewer courses of standard radiotherapy (1.3 vs 1.8 courses; p=0.0291), but were more likely to be receiving radiotherapy at time of data collection (40% vs 22%; p=0.004) (Table 3)
  - Physicians perceived that radiotherapy had an overall positive impact on the patients quality of life in more MGMT-tested patients than MGMT-untested patients (65% vs 47%; p=0.0431) (Data not shown)
- Non-drug treatments for MGMT promotor-methylated vs MGMT promotor-unmethylated patients showed no statistically significant differences, the same was true for active drug treatments. MGMT promotor-methylated patients received more non-opioid analgesics (38% vs 23%; p=0.039) and opioid analgesics (42% vs 21%; p=0.0063) than MGMT promotor-unmethylated patients (data not shown), and were on their 1L treatment for longer (12.9 vs 8.8 weeks; p=0.0256) at time of data collection
- Overall, most patients were responding to treatment (30%) or had a stable disease (59%) (Figure 3)
- MGMT-tested patients were more likely to be responding to treatment (33% vs 27%) or have a stable disease (60% vs 57%) than MGMT-untested patients (p=0.0326) (Figure 3). No statistically significant differences were observed between groups for physician-perceived prognosis at time of data collection (Figure 4)
- No statistically significant differences were observed for response status between MGMT promotor-methylated and MGMT promotor-unmethylated patients (Figure 3), however physician-perceived prognosis at time of data collection was longer for MGMT promotor-methylated patients (77.4 vs 61.1 weeks; p=0.0333) (Figure 4)

Table 2. Clinical Characteristics for 1L GBM patients that completed a PSC

	Total	MGMT Untested	MGMT Tested	Methylated	Unmethylated	p-value
	326	152	174	91	83	
ECOG score at time of consultation, n (%)						
0	43 (14.7)	17 (14.4)	26 (14.9)	16 (17.6)	10 (12.0)	1: 0.0005 2: 0.3808
1	143 (49.0)	43 (36.4)	100 (57.5)	48 (52.7)	52 (62.7)	
2+	106 (36.3)	58 (49.2)	48 (27.6)	27 (29.7)	21 (25.3)	
Grade of tumor at diagnosis, n (%)						
Grade I Pilcytic astrocytoma	17 (5.5)	15 (11.0)	2 (1.2)	2 (2.2)	0 (0.0)	1: <0.0001 2: 0.1804
Grade II Diffuse / Low-grade astrocytoma	22 (7.1)	16 (11.8)	6 (3.5)	5 (5.5)	1 (1.2)	
Grade III Anaplastic astrocytoma	19 (6.1)	13 (9.6)	6 (3.5)	4 (4.4)	2 (2.4)	
Grade IV Glioblastoma (de novo GBM)	251 (81.2)	92 (67.6)	159 (91.9)	80 (87.9)	79 (96.3)	
Form of GBM						
Unifocal GBM (solitary tumor)	213 (71.0)	72 (57.1)	141 (81.0)	79 (86.8)	62 (74.7)	1: <0.0001 2: 0.0529
Multifocal GBM (multiple tumors)	87 (29.0)	54 (42.9)	33 (19.0)	12 (13.2)	21 (25.3)	
Resectability of tumor at diagnosis, n (%)						
Resectable at diagnosis	185 (56.7)	67 (44.1)	118 (67.8)	69 (75.8)	49 (59.0)	1: <0.0001 2: 0.0202
Non-resectable at diagnosis	110 (33.7)	58 (38.2)	52 (29.9)	19 (20.9)	33 (39.8)	
Not eligible for resection	31 (9.5)	27 (17.8)	4 (2.3)	3 (3.3)	1 (1.2)	
Time since diagnosis, weeks						
Mean (SD)	17.5 (17.5)	20.1 (22.1)	16.4 (15.1)	19.5 (18.6)	13.2 (9.5)	1: 0.1735 2: 0.0156
Median	13.3	14.6	13.0	14.6	11.0	

1: P-value for MGMT untested vs MGMT tested; 2: P-value for MGMT promotor methylated vs MGMT promotor unmethylated

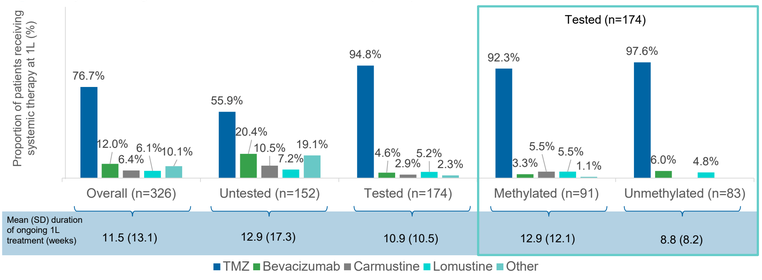
Figure 1: Non-drug treatments ever received



P-values comparing MGMT tested vs untested and MGMT promotor methylated vs unmethylated

	Surgery	Radiotherapy	Tumor-treating fields	None
MGMT tested vs untested	< 0.0001	< 0.0001	0.362	< 0.0001
MGMT promotor methylated vs unmethylated	1	0.6607	0.5969	0.6061

Figure 2: Systemic drug treatment received at 1L and duration (weeks) of treatment



P-values comparing MGMT tested vs untested and MGMT promotor methylated vs unmethylated

	TMZ	Bevacizumab	Carmustine	Lomustine	Other
MGMT tested vs untested	< 0.0001	< 0.0001	0.0006	0.4927	<0.0001
MGMT promotor methylated vs unmethylated	0.1725	0.4811	0.0602	1	1.1223

Figure 3: Response to treatment at 1L

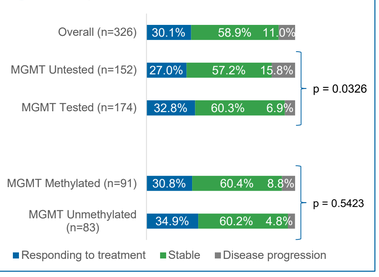


Figure 4: Mean (SD) physician-reported estimation of patient prognosis (physician-perceived prognosis) (weeks) at time of data collection

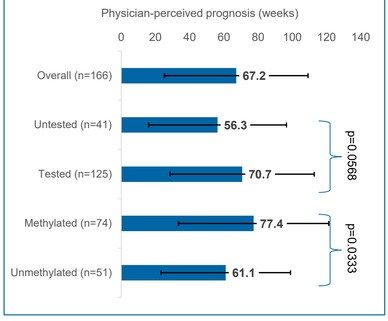


Table 3. Radiotherapy administered alongside 1L

Mean (SD) courses of standard radiotherapy		p-value	Number (%) of patients continuing to receive radiotherapy at time of data collection		p-value
Overall (n=190)	1.4 (1.5)		n=169	62 (36.7)	
MGMT Untested (n=45)	1.8 (2.1)	0.0291	n=32	7 (21.9)	0.0004
MGMT Tested (n=145)	1.3 (1.3)		n= 137	55 (40.1)	
Methylated (n=72)	1.4 (1.5)	0.2206	n= 66	22 (33.3)	0.0945
Unmethylated (n=73)	1.1 (1.1)		n= 71	33 (46.5)	

Strengths and limitations

- Key strengths of this study are the large sample size and data collection based on a validated, previously published methodology[7]
- The quality of data depends to a large extent on the accurate reporting of information by physicians
- Due to data being collected at one point in time, it cannot be used to demonstrate cause and effect. However, this is not the intended purpose of the DSP

Conclusions

- Nearly half of newly diagnosed GBM patients were not MGMT tested in the US
- MGMT-tested patients were more likely to receive radiotherapy, surgery and TMZ and had better treatment response than untested patients
- MGMT promotor-methylated patients had better physician-perceived prognosis, were more likely to be resectable at diagnosis and received systemic treatment for longer than MGMT promotor-unmethylated patients
- MGMT-tested patients received similar systemic treatments regardless of MGMT promotor-methylation status
- Improvement of MGMT-testing rates is needed and there is an unmet treatment need for precision medicines based on MGMT promotor-methylation status

Table 1. Demographics for 1L GBM patients at time of data collection

	Overall (n=326)	MGMT Untested (n=152)	MGMT Tested (n=174)	Methylated (n=91)	Unmethylated (n=83)	Test	p-value
Patients age							
Mean (SD)	60.3 (14.6)	60.9 (16.1)	59.7 (13.1)	58.9 (13.8)	60.5 (12.4)	(TT)	1:0.4458 2: 0.4092
Median	61	61	61	61	61		
Patients gender							
Male, n (%)	211 (64.7)	88 (57.9)	123 (70.7)	65 (71.4)	58 (69.9)	(FE)	1: 0.02 2: 0.8684
Patients' alcohol consumption							
Binge - Regular heavy drinker	11 (3.4)	10 (6.6)	1 (0.6)	1 (1.1)	0 (0.0)	(CH)	1: <0.0001 2: 0.7099
Regular drinker	21 (6.4)	11 (7.2)	10 (5.7)	6 (6.6)	4 (4.8)		
Occasional drinker	72 (22.1)	27 (17.8)	45 (25.9)	21 (23.1)	24 (28.9)		
Infrequent drinker	69 (21.2)	25 (16.4)	44 (25.3)	24 (26.4)	20 (24.1)		
Non-drinker / abstinent	94 (28.8)	39 (25.7)	55 (31.6)	27 (29.7)	28 (33.7)		
Don't know	59 (18.1)	40 (26.3)	19 (10.9)	12 (13.2)	7 (8.4)		
BMI							
Mean (SD)	26.5 (4.6)	26.9 (5.4)	26.2 (3.8)	26.3 (4.1)	26.0 (3.4)	(TT)	1: 0.1372 2: 0.5915
Median	25.9	26.4	25.8	25.8	25.8		
US Region							
West	41 (12.6)	31 (20.4)	10 (5.7)	7 (7.7)	3 (3.6)	(CH)	1: <0.0001 2: 0.3213
Midwest	61 (18.7)	33 (21.7)	28 (16.1)	13 (14.3)	15 (18.1)		
South	106 (32.5)	54 (35.5)	52 (29.9)	31 (34.1)	21 (25.3)		
Northeast	118 (36.2)	34 (22.4)	84 (48.3)	40 (44.0)	44 (53.0)		
Patients' ethnicity							
White/Caucasian	227 (69.6)	90 (59.2)	137 (78.7)	75 (82.4)	62 (74.7)	(CH)	1: 0.0019 2: 0.6192
African American	50 (15.3)	30 (19.7)	20 (11.5)	8 (8.8)	12 (14.5)		
Hispanic / Latino	26 (8.0)	17 (11.2)	9 (5.2)	4 (4.4)	5 (6.0)		
Other	23 (7.1)	15 (9.9)	8 (4.6)	4 (4.4)	4 (4.8)		

1: P-value for MGMT untested vs MGMT tested; 2: P-value for MGMT promotor methylated vs MGMT promotor unmethylated; TT = t-test, FE = Fisher's Exact test, CH = Chi-squared test

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