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Chemotherapy toxicities and geriatric syndromes in older patients with malignant gliomas

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ABSTRACT

Objective: To describe treatment toxicities and polypharmacy in older patients with malignant gliomas (MG).
Background: Advanced age in cancer patients is associated with increased treatment-related toxicities, acute care utilization and functional decline. Most patients with MG are over age 65, yet treatment patterns and toxicities are poorly defined.
Methods: A retrospective chart review of 125 patients with MG age 65 or older at the University of Rochester from January 2012 to December 2018.
Results: 115 patients with glioblastoma and 10 with anaplastic astrocytoma had a median age of 71 (range 65–89) at diagnosis and median overall survival (OS) of 10.3 months. Radiotherapy (RT) was offered and completed in 79% (fractionated, $n = 69$, hypofractionated, $n = 30$). 24% of the 98 patients treated with concurrent temozolomide (TMZ) experienced treatment delays ($n = 24$). Median of 4 cycles of adjuvant TMZ were taken by 61% ($n = 76$). Delays and dose reductions occurred in 55% during treatment with adjuvant TMZ, most commonly due to thrombocytopenia ($n = 29$) and fatigue ($n = 15$). 16/98 patients required transfusions during treatment with concurrent or adjuvant TMZ. At baseline, patients were prescribed a median of 11 medications. OS was longer in patients prescribed less than 8 medications vs. 8 or more (14 vs. 8.6 months, $p = .0738$). 96% experienced a non-elective hospital admission and 64% reported at least one fall.
Conclusion: Older patients with MG experience significant polypharmacy, treatment toxicities and falls. Studies incorporating geriatric assessment tools may better determine associations between geriatric syndromes and survival. Clinical trials in older patients should also include non-survival outcomes.

1. Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumor in older adults and has a significant impact on survival, neurologic function, psychological health and quality of life [1–3]. GBM is increasing in incidence among older patients, and increased age has been associated with decreased overall survival [4]. The current standard of care for treatment of GBM includes maximally safe surgical resection followed by radiation and alkylating chemotherapy with temozolomide (TMZ), with a median survival of 14.6 months in patients under the age of 65 [5]. Patients over the age of 65 comprise approximately 40% of the GBM population yet remain undertreated, with nearly 30% receiving no treatment or less than standard care [3,6]. Oncologic clinical trials have historically excluded adults with medical comorbidities or those over 70 years of age, with only a few clinical trials specifically designed to study this population [7]. In two multi-center randomized clinical trials, a shorter course of radiotherapy (SCRT) of 40 Gy in 15 fractions was shown to be at least as effective as longer-course radiotherapy [8,9]. SCRT is often preferred in older or frail patients given improved tolerability and convenience and is widely accepted as standard of care in patients over the age of 65. Concurrent treatment with TMZ during radiotherapy is recommended for patients with good functional status, but TMZ treatment is often withheld in patients with impaired performance status or an unmethylated O^6-methylguanine-DNA methyltransferase (MGMT) promoter, which has been associated with relative insensitivity to chemotherapy and decreased survival [10].

Advanced age in patients with systemic cancer or glioblastoma has been associated with increased treatment-related toxicities, acute care utilization and functional decline [11–13]. Hurria et al. showed that older patients receiving chemotherapy for any cancer type have a high prevalence of grade 3 or higher toxicity by NCI Common Toxicity Criteria, occurring in 53% of patients [11]. Risk factors for grade 3–5 toxicity included age 73 or older, polychemotherapy, falls, assistance required with instrumental activities of daily living and low social activity. Reporting of toxicities for older patient GBM clinical trials has

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focused on neurologic symptoms, fatigue, hematologic and hepatic toxicities, and the frequency and severity of adverse events is similar to those of younger patients. This older clinical trial population may not reflect the true experience of older patients with MG in the community. We sought to describe the treatment related toxicities and geriatric syndromes occurring in a cohort of older patients with MG at a single academic neuro-oncology center.

2. Methods

We conducted an institutional review board (IRB) approved study of patients age 65 or older with pathologically confirmed malignant gliomas (MG) who were seen at the University of Rochester Medical Center (URMC) from January 1st, 2012 to December 31st, 2018. Consecutive patients with pathologically proven anaplastic astrocytoma (AA) and GBM were included in the analysis. These patients were identified from a neuro-oncology database that consisted of patients who received their primary oncologic care at URMC. Demographic information collected included age at diagnosis, date of diagnosis, date of death, extent of surgical resection and performance status at diagnosis. Overall survival (OS) was calculated as time from diagnosis to death. Progression free survival (PFS) was calculated as time from pathologic diagnosis to first progression based on Response Assessment in Neuro-Oncology (RANO) criteria [14]. Tumor-specific information including histopathologic diagnosis and tumor grade, isocitrate dehydrogenase (IDH) status and O^6-methylguanine-methyltransferase (MGMT) promoter methylation status were also recorded.

Treatment with radiotherapy and concurrent and adjuvant use of temozolomide chemotherapy were documented from the electronic medical record. Radiotherapy was considered hypofractionated when a dose of 40 Gy was administered in 15 fractions. Standard course radiotherapy was documented as a dose of 60 Gy administered in 30 fractions. Radiotherapy was considered incomplete if a patient did not receive 3 or more fractions of planned treatment. Any delays or disruptions in chemotherapy or radiotherapy and the reasons for such were assessed. The number of days of concurrent TMZ completed and total number of completed cycles of adjuvant TMZ were recorded. The length and etiology of delays and/or disruptions in chemotherapy treatment were also evaluated. Chemotherapy was considered delayed if a cycle of TMZ began 7 or more days following the scheduled cycle start date. Records were also analyzed for hematologic toxicities and when applicable, the number and type of blood product transfusions administered. Use of second line therapeutic agents, the Optune (Novo-TTF) device and clinical trial enrollment was also evaluated.

The number of prescribed medications at the time of the first neuro-oncology clinic visit was documented and the use of antidepressants or corticosteroids at any point following diagnosis was recorded. All active medications at time of diagnosis were also cross-referenced with Beer's Criteria for potentially inappropriate medication use in older adults [15]. Acute care utilization including emergency visits and hospital admissions was also documented. Emergency visits were defined as occasions where patients had an encounter with the emergency department without hospital admission. A hospital admission was defined as any hospital encounter resulting in an admission to a medical or intensive care unit. The electronic medical record was also reviewed for whether patients had experienced falls and whether active hospice services were in place at time of death.

3. Results

3.1. Patient demographics and tumor characteristics

We identified 125 patients with histopathological diagnosis of MG: 115 with GBM, 10 with AA. The median age at diagnosis was 71. Survival data was available for 117 patients who had a median overall survival (OS) of 10.3 months. Median progression free survival was 5.7 months ($n = 110$). Patient demographics and tumor characteristics are shown in Table 1. AA patients were included in the analysis as 80% had a molecular phenotype (lack of isocitrate dehydrogenase mutation) and survival similar to GBM. 96% of patients experienced at least one hospital admission during their disease course (range: 1–3). The most common reasons for hospital admission were seizures followed by progressive neurologic symptoms and venous thromboembolism. Falls were common and occurred in 64% of patients. At time of death, 83% of patients were enrolled on hospice. At time of data analysis, 96% of patients ($n = 120$) had died.

Table 1
Patient characteristics.

	Patients ($n = 125$)	
Gender	No.	%
Female	53	42.4
Male	72	57.6
Median Age at Diagnosis	71 (65–89)	
Age at Diagnosis	No.	%
65–70	49	39.2
71–75	35	28.0
76–80	24	19.2
81–85	12	9.6
86+	5	4.0
Median KPS at Diagnosis	80 (40–100)	
% of Patients with KPS > 70	53.6%	
Pathologic and Molecular Characteristics	No.	%
Glioblastoma	**115**	**92.0**
IDH wildtype	94	75.2
IDH mutant	3	2.4
IDH indeterminate	4	3.2
IDH unknown	14	11.2
Anaplastic Astrocytoma	**10**	**8.0**
IDH wildtype	8	6.4
IDH mutant	1	0.8
IDH indeterminate	0	0
IDH unknown	1	0.8
MGMT status		
MGMT methylated	38	30.4
MGMT unmethylated	57	45.6
MGMT indeterminate	5	4.0
MGMT unknown	25	20.0
Degree of Surgical Resection	No.	%
Biopsy	36	28.8
Subtotal	54	43.2
Gross total	35	28.0
Median survival (months)	10.3	
Glioblastoma	10.2	
Anaplastic Astrocytoma	10.8	
Death	No.	%
	120	96.0

KPS = Karnofsky Performance Status, IDH = isocitrate dehydrogenase, MGMT = O^6-methylguanine-methyltransferase.

3.2. Chemoradiotherapy and treatment toxicities

Summary of treatment patterns and toxicities can be found in Table 2. Radiotherapy (RT) was offered to 84% of patients ($n = 105$). Standard RT (60 Gy in 30 fractions) was offered in 75 patients and hypo-fractionated RT was offered in 30 patients. Patients treated with standard RT received a median of 27 fractions, although 8% (6/75) did not complete the regimen. All patients treated with hypo-fractionated RT completed treatment. 78% of patients ($n = 98$) received concurrent TMZ. One-quarter (24/98) of patients experienced a treatment delay or discontinuation during treatment with concurrent TMZ. Seven patients discontinued treatment with concurrent TMZ due to prolonged thrombocytopenia. The major reasons for delay or discontinuation in concurrent TMZ were thrombocytopenia, fatigue and neurologic or functional decline.

61% of patients ($n = 76$) were treated with adjuvant TMZ, receiving a median of 4 cycles. 55% of those patients ($n = 41$) experienced a delay or

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Table 2
Treatment characteristics of older patients with malignant gliomas.

	Patients treated	
No Treatment Received	20/125	16%
Radiation (n = 105)	105/125	84%
60 Gy/30 fractions		
Completed	69/75	92%
Not completed	6/75	8%
40 Gy/15 fractions		
Completed	30/30	100%
Concurrent Chemotherapy (*n* = 98)		
Completed concurrent TMZ	74/98	76%
Concurrent TMZ not completed	24/98	24%
Adjuvant Chemotherapy (*n* = 76)		
Median # of cycles of TMZ completed	4 cycles	
# of patients completing at least 6 cycles of TMZ	46/76	60%
# of patients with treatment delays	41/76	54%
Chemotherapeutic toxicities (*n* = 98)*		
Thrombocytopenia	29/98	30%
Grade 3 thrombocytopenia	13/98	14%
Grade 4 thrombocytopenia	16/98	16%
Fatigue	18/98	18%
Neurologic or functional decline	17/98	17%
Treatment at Time of Progression (*n* = 125)		
Patients treated with Bevacizumab	58/125	47%
Patients enrolled on a clinical trial	11/125	9%
Hospice in place at time of death	104/125	83%
Polypharmacy (*n* = 125)		
Median # of prescription medications at diagnosis	11	
Median # of new medications prescribed during treatment	4	
Overall survival with <8 prescribed medications	14 months	
Overall survival with >/= 8 prescribed medications	8.6 months	
Supportive Care Medications Prescribed During Treatment		
Antidepressant	68/125 (54%)	
Corticosteroid	124/125 (99%)	
Proton pump inhibitor	124/125 (99%)	
Anti-emetic	100/125 (80%)	
Anti-epileptic	51/125 (41%)	
Patients with medications on Beer's List at diagnosis**	38/125 (30%)	

TMZ = temozolomide; *Toxicities resulting in dose reductions or delays in treatment.

dose reduction during treatment with adjuvant TMZ, most commonly due to thrombocytopenia ($n = 15$) and fatigue ($n = 15$). Other reasons for delays included failure to thrive and neurologic deterioration.

Hematologic toxicity was common and Grade 4 thrombocytopenia, defined as platelet count <25,000/mm^3 occurred in 16% of patients ($n = 16/98$) receiving concurrent or adjuvant TMZ. All 16 patients received platelet transfusions and 1 patient also required transfusion of packed red blood cells. At time of disease progression, 47% of patients (58/125) were treated with bevacizumab. Tumor treating fields (Novo-TTF device) were used in 29% of patients (36/125). 9% of patients were enrolled on a clinical trial ($n = 11/125$).

3.3. Polypharmacy

Patients were prescribed a median of 11 medications at time of diagnosis. Median OS for those prescribed 8 or more medications was 8.6 months and 14 months for patients prescribed less than 8 medications ($p = .0738$). Fig. 1 shows the Kaplan Meier survival curve for patient taking fewer than 8 medications vs. 8 or more medications. Patients aged 70–74 were prescribed the highest amount of medications, with a median of 12 prescriptions at their first neuro-oncology clinic visit. Thirty percent of patients ($n = 38/125$) were prescribed at least one medication meeting Beers Criteria for potentially inappropriate medication use in older adults. During their treatment course patients were prescribed a median of 5 additional medications, most commonly TMZ, corticosteroids, anti-emetics, anti-epileptic drugs, antidepressants and sleep aides. Nearly all patients (99.2%) received corticosteroids during their treatment. Half of the patients (54%) were prescribed an antidepressant at any point following their initial consultation ($n = 68/125$).

4. Discussion

Our study demonstrates that treatment related toxicities are common in older patients, who frequently experience falls and polypharmacy, with limited survival. Glioblastoma clinical trials focused exclusively on older patients such as the Nordic trial and the study of Perry et al. showed median survivals between 8 and 9 months, which is consistent with the median survival of our patient cohort of 10.3 months [9,16]. While overall survival was largely similar, it was higher in our cohort and this may be due to the presence of 10 patients

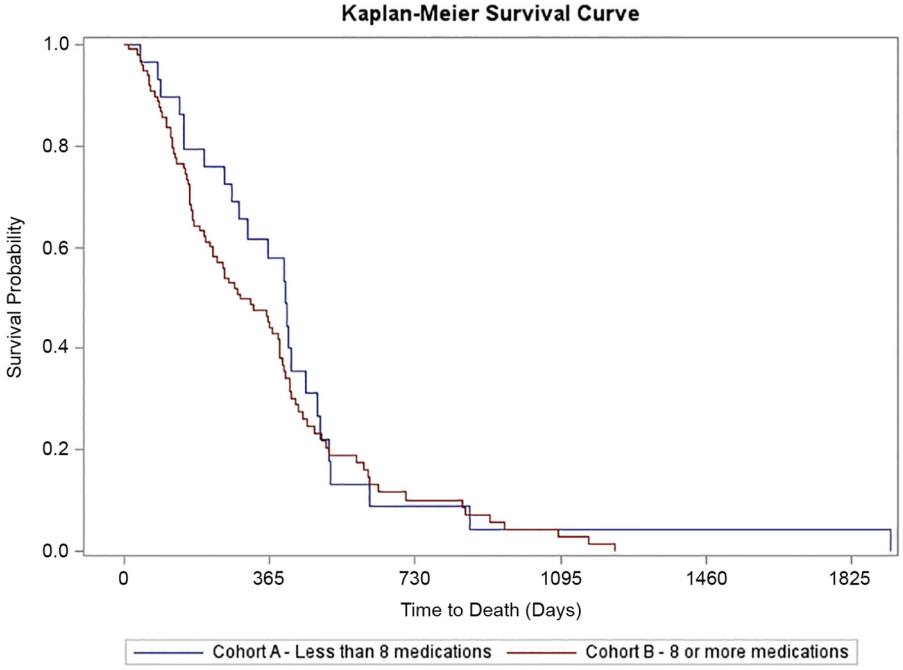

Fig. 1. Polypharmacy and survival of older patients with malignant glioma.

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with anaplastic astrocytoma, most patients receiving standard RT and the use of tumor treating fields. Our key finding was that the rate of treatment related toxicities in this patient population is much higher than reported in prospective clinical trials. This is consistent with other reports demonstrating that standardized adverse event reporting in clinical trials underestimates symptoms experienced by patients [17]. Treatment related toxicities were likely more common in our study due to presence of additional medical comorbidities, decreased performance status and older age of real-world patients compared to clinical trial participants. Our data demonstrate that toxicities are common and may be severe, necessitating dose reduction, cessation of treatment, additional medical intervention or hospitalization. The most common toxicities of TMZ including fatigue and thrombocytopenia may significantly limit the function and quality of life of older patients. The survival benefit of TMZ is largely seen in those with MGMT-methylated promoters [9,16], and the omission of TMZ for unmethylated patients should be considered for older patients as treatment exposes them to risk of toxicities with marginal benefit [18]. Grade 3 and 4 thrombocytopenia occurred two to three times more frequently in our cohort compared to that reported by Perry et al. in a trial of hypofractionated RT and TMZ (5.9% vs, 14% and 5.1% vs 16% respectively) [9]. The potential underestimation of toxicities in clinical trial populations of older patients can alter the perceived risk and benefit ratio when making treatment decision and it is important to both be more inclusive of all older patients on brain tumor clinical trials and to prospectively collect toxicity data on patients who might be ineligible for clinical trials. Without this information, we lack a true picture of toxicity from our most commonly used regimens in the treatment of malignant gliomas.

The use of performance scales such as the Karnofsky Performance Status (KPS) or Eastern Cooperative Oncology Group (ECOG) performance status are frequently used to determine a patient's fitness for treatment. The scales are neither sensitive nor specific and have limitations in patients with MG, as they may not capture the true functional abilities of patients with neurologic symptoms and are unable to capture small changes in function [19]. Enhanced assessments such as the comprehensive geriatric assessment (CGA) can be informative tools for identifying frailty and predicting treatment risk. CGA uses multiple validated tools to assess the geriatric domains of comorbidities, functional and psychological status, cognition, physical performance, nutrition, medication reconciliation and social support [20], and has been shown to detect unsuspected conditions that may affect cancer treatment in over 50% of older patients with systemic cancer [21]. National Comprehensive Cancer Network guidelines for Senior Adult Oncology also recommend that all older patients with cancer undergo a CGA [22]. CGA can be helpful in identifying underlying medical, functional and psychosocial issues that may limit or interrupt treatment and allows for more individualized treatment planning. Retrospective review of a large cohort of older patients with glioblastoma showed that CGA score was an independent predictor of mortality [23]. Further prospective studies on the utility of CGA in primary brain tumors are needed.

Our data also highlight the significant polypharmacy that many older patients with MG experience. It is well established that in patients with a cancer diagnosis, additional comorbidities or polypharmacy are associated with a poorer overall survival [24], and our study showed inferior survival benefit for patients taking 8 or more medications. The magnitude of polypharmacy observed likely also reflected the presence of additional medical comorbidities that may negatively impact survival. Older patients are at increased risk of polypharmacy including drug-drug interactions, toxicities and medication errors due to increased sensitivity, decreased metabolism and medication volume. Patients with brain tumors may be particularly sensitive to the compounding effects of centrally acting medications and at an increased risk of confusion, fatigue and falls. This is of particular concern in older patients, such as the 30% in our cohort who were prescribed drugs meeting Beers criteria for inappropriate use in older adults. These findings, in the setting of a terminal illness, highlight the need to re-evaluate prescribed medications and to consider de-escalation of non-essential drugs.

Patients in our cohort were prescribed a median of 4 additional medications during treatment, adding to existing polypharmacy. Nearly all patients required corticosteroids at some point during their course, which may cause a host of toxicities including weight gain, mood disturbance, sleep dysregulation and proximal myopathy potentially leading to falls. The toxicities of corticosteroids are frequently amplified in older patients and should be considered at the lowest dose and for the shortest duration required to control neurologic symptoms. Aggressive corticosteroid toxicity monitoring and tapering protocols should be considered for this population.

Seizures were the most common reason for hospital admission for our cohort and are the frequent reason for acute care utilization in patients with MG [13]. Current guidelines do not support the use of antiepileptic medications for seizure prophylaxis and in clinical practice are only started once a patient with MG experiences a seizure [25]. Older patients are at particular risk for side effects from antiepileptic medications including sedation, ataxia, falls and pharmacologic interactions with chemotherapy. Most seizures are brief and self-limited and can be safely taken care of at home or in the outpatient setting. Structed and focused education for patients and caregivers regarding tumor-related epilepsy (TRE) should be considered in the older patients with MG population. TRE specific education has been shown to be feasible and to decrease seizure-related distress for patients and caregivers [26], and may be an effective strategy for reducing acute care utilization in this population.

Depression was a common comorbidity with 54% of patients being prescribed an anti-depressant following diagnosis. Antidepressants are most commonly prescribed for treatment of depression but can be used for other indications including neuropathic pain and headaches. Using the prescription of an antidepressant as a surrogate for a depression diagnosis may have overestimated the prevalence of depression in this cohort. Depression is the most common geriatric syndrome among older cancer patients receiving chemotherapy [27] and has been shown to negatively impact the care, medication compliance and survival of patients with GBM [28].

Depression is often underreported and thus underdiagnosed and undertreated in older adults and in patients with brain tumors. Given the prevalence of depression in this population, providers should elicit symptoms of depression at each clinical encounter. Additionally, patients may benefit from the longitudinal use of a validated screening tool such as the Geriatric Depression Scale [29].

Falls were a common complication during MG treatment with 64% of patients reporting at least one fall. Falls are common in patients with brain cancer due to neurologic impairment and polypharmacy and have been associated with increased acute care utilization and decreased survival in cancer patients [30]. All older patients should have a fall risk assessment and appropriate interventions in the event of falls [31]. Physical therapy, occupational therapy, orthotics and assistive devices for ambulation should all be considered. A thorough medication review and neurologic examination to assess for contributing factors (such as polypharmacy, hemiparesis or corticosteroid-induced proximal myopathy) should be done in any patient presenting with a fall. Nearly all patients experienced at least one hospital visit following diagnosis, which have been associated with decreased quality of life, iatrogenic complications and survival [32]. Appropriate choice of treatment with attention to toxicities, polypharmacy and fall prevention may help limit acute care utilization in this population.

The major strengths of this study are the large patient sample and that most patients received all their care locally at our institution, allowing for comprehensive and longitudinal data collection. This study evaluated older adults in the community, not just clinical trial candidates, and our findings may be more representative of the general population. The study used objective data on medications and polypharmacy found in the electronic medical record. Limitations of

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this study include its retrospective nature, which due to missing data may actually underestimate toxicities, falls and polypharmacy. Another limitation is the use of Beers Criteria, which is less sensitive than other instruments assessing medication inappropriateness in older adults (such as STOPP-START and the Medication Appropriateness Index) [33]. The use of this tool may have under- or overreported polypharmacy in this population. While documentation of falls was institutionally required at the time of each clinic visit, the use of the electronic medical record for this is not the gold standard and may have led to underreporting of falls. Additionally, minimal information was available regarding quality of life and patient-reported outcomes, both important metrics that should be considered in the care of older MG patients.

5. Conclusion

Older adults with MG experience frequent treatment toxicities and comorbidities despite living less than a year following diagnosis. Stannard treatment with radiation and temozolomide result in nominal survival benefits while exposing patients to toxicities which may impair their quality of life and physical function. More work is needed to better understand the geriatric MG patient, to determine those who are appropriate for treatment and to reduce treatment related risks. Clinical trials may need to consider outcome measures other than survival, which may be more meaningful to older patients. Additionally, increasing the enrollment of older patient on therapeutic clinical trials and creating trials to address this population are critical given their unique risks.

Author contributions

Author	Contribution
Andrea Wasilewski MD[1]	Manuscript conception, Data Analysis, manuscript drafting, editing and review
Ahmar Alam[2]	Data analysis, manuscript drafting
Nimish Mohile MD[3]	Manuscript conception, manuscript editing and review

Declaration of Competing Interest

Andrea Wasilewski reports consulting fees from Novocure.
Ahmar Alam reports no disclosures.
Nimish Mohile reports no disclosures.

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