Review Article
A review of management strategies of malignant gliomas in the elderly population

Priya U Kumthekar[1], Bryan D Macrie[2], Simran K Singh[1], Gurvinder Kaur[3], James P Chandler[3], Samir V Sejpal[2]

Departments of [1]Neurology, [2]Radiation Oncology, [3]Neurosurgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

Abstract: Glioblastoma Multiforme (GBM) is the most frequent primary malignant brain tumor in adults. It is an aggressive primary brain neoplasm, associated with a poor prognosis and median survival of less than 1 year. Approximately 50% of patients diagnosed with malignant gliomas in the United States are over the age of 65. Advancing age and poor performance status are two variables that have found to negatively affect prognosis. When compared to younger patients, not only is the treatment of elderly patients associated with decreased efficacy but also greater toxicity. As a result, elderly patients often receive less aggressive treatment and are excluded from clinical trials. There are many challenges in the treatment of elderly patients with GBM including increased surgical morbidity and mortality as well as increased toxicity to radiation and chemotherapy. As such, the optimal therapy remains unclear and controversial for the elderly malignant glioma population.

Keywords: High grade glioma, GBM, MGMT, malignant astrocytoma, elderly patients

Introduction

Glioblastoma Multiforme (GBM) is the most frequent primary malignant brain tumor in adults [1]. It is an aggressive primary brain neoplasm associated with a poor prognosis. Median survival is less than 1 year [2]. Approximately 50% of patients diagnosed with malignant gliomas in the United States are over the age of 65 [3]. The current standard of care for younger GBM patients with adequate performance score consists of maximal safe surgical resection followed by standard fractionation involved-field Radiation Therapy (RT) with daily oral alkylating chemotherapy temozolamide (TMZ). Stupp and colleagues demonstrated a 37% relative reduction in the risk of death at 5-years in patients treated with this regimen as compared to those treated with adjuvant involved field radiotherapy alone. While this study included only patients under the age of 70, subgroup analysis showed that this benefit persisted for the patient cohort aged 61-69 [4].

Many questions remain regarding the role of chemotherapy concurrent with radiation in the management of elderly patients with GBM [4,

5]. Advancing age and poor performance status are two variables that have found to negatively affect prognosis [3]. The 2-year survival in patients age 65 and above is 2.1%, compared to 7.7% and 29.9% in patients aged 45-64 and 20-44 respectively [6]. When compared to younger patients, not only is the treatment of elderly patients associated with decreased efficacy but also greater toxicity. As a result, elderly patients often receive less aggressive treatment and are excluded from clinical trials [7]. There are many challenges in the treatment of elderly patient with GBM including increased surgical morbidity and mortality as well as increased toxicity to radiation and chemotherapy. As such, the optimal therapy remains unclear and controversial for the elderly malignant glioma population.

Surgical considerations in the elderly

Gross total resection in both primary and recurrent GBM has been found to independently improve survival [8, 9]. In the elderly population, a small randomized trial of 23 patients 65 years or older indicated that surgical resection was associated with longer survival compared

to biopsy [10]. Another series evaluated 88 patients 65 years or older who had biopsy only versus surgical resection. A modest improvement in survival (27 wks vs. 15 wks) was seen in in the surgical resection group [11] showed a survival benefit of 5.7 months vs. 4 months for surgical resection compared to biopsy in patients 65 years or older (median age of 73) [12]. Iwamoto et al. found a 60% reduction in risk of death after a gross total resection in comparison to partial resection in 394 patients with a median age of 72 [13].

Although surgical resection significantly improve survival over biopsy alone, surgery as primary treatment for GBM in a group that is likely to have high-risk co-morbidities due to age can be challenging [16]. Primary care data shows that of the patients in the age group of 75-84, 19% of men and 12% of women have some degree of cardiovascular disease (CVD) [14]. Thus, thorough geriatric preoperative risk assessment and risk strategies for operative and post-operative risk reduction becomes especially relevant in this group.

Radiation therapy alone in the elderly

Radiation therapy is a common treatment modality in elderly patients and has been studied in both standard and abbreviated courses. As elderly patients are often observed to have decreased tolerability to a six week radiation course [5], recent trials have looked at the value of modifying radiation treatment time as well as TMZ as monotherapy. "Elderly" patients have been inconsistently defined in these studies as some have used age > 60 while others have used a cut-off of 65 or 70. Karnofsky Performance Status (KPS) cutoff has also been inconsistent and as such these parameters should be reconsidered with each individual treatment trial evaluating elderly patients with malignant gliomas. To date, two randomized controlled trials that have addressed the efficacy and tolerability of RT alone in the elderly population.

The first trial established a survival benefit of RT over supportive care. In this French study by Keime-Guibert and colleagues, 85 patients at 10 French institutions were enrolled between 2001 and 2005. Eligible patients had newly diagnosed GBM or Anaplastic Astrocytoma (AA), were 70 years or older, and had a KPS score of 70 or higher. After surgical manage-

ment, patients were assigned to receive either involved-field RT (50.4 Gy in 1.8 Gy fractions given 5 days per week) with best supportive care versus best supportive care alone. The treatment volume in the radiation arm included the contrast enhancing tumor seen on MRI plus a 2-cm margin. In both study arms, the majority of patients had biopsy only (52% v 51%, RT v. supportive care) prior to randomization. At a median follow up time of 21 weeks, there was a statistically significant 53% relative reduction in the risk of death for the 39 patients who received RT compared to supportive care only. Median survival was 29.1 weeks in RT plus supportive care arm compared to 16.9 weeks in the supportive care arm (HR: 0.47; 95 CI: 0.29-0.76; p = 0.0002). Analyses of health-related quality of life (QOL) performed on days 1, 30, 60, 90, and 135 were not statistically significant between treatment groups. Likewise, cognitive evaluations, also limited to 135 days follow-up, did not differ between arms [15].

The second trial, by Roa et al in Canada, demonstrated comparable survival between a sho_rtened hypofractionated (HF) RT course using fractions greater than 2 Gy per day for 3 weeks compared to the standard course ousing fraction size of 2 Gy per day given over 6 weeks. In a this study, 100 patients aged 60 years and older from 4 Canadian centers were randomly assigned to receive either standard post-operative radiation therapy to 60 Gy in 30 fractions over 6 weeks versus a biologically equivalent HF course of 40 Gy in 15 fractions over 3 weeks. Extent of surgery was comparable in both arms with subtotal resection in 52.3% of patients on the standard arm versus 50.0% in the shortened arm. In the standard arm, 46 Gy in 23 fractions was delivered to a volume consisting of enhancing tumor and peri-tumoral edema plus a 2-2.5 cm margin. A 14 Gy boost in 7 fractions was then delivered to the enhancing tumor plus 2.5 cm margin. The volume treated in the hypofractionated arms was equivalent to that used in the first phase of the standard treatment. There was no statistically significant difference in median overall survival of 5.1 months vs. 5.6 months (p = 0.57) in the two treatment arms and fewer patients required an increase in post-treatment corticosteroid dose (23% vs. 49%) in the HF-RT group. Health-related QOL was not directly evaluated, but there was no significant difference in KPS scores between arms through six-months after the start of RT [16].

In addition to these randomized trials, retrospective analyses of elderly patients treated with standard RT have shown survival ranging from 4 to 8 months [6]. In light of the inferior prognosis for elderly individuals with GBM, treatments intended to prolong survival need to be limited in toxicity and total duration otherwise the potential benefit may be negated by reduced quality of life. With the exception of one case of transient somnolence after the completion of therapy, RT was very well tolerated in the multi-center French study [15]. However, the 6 weeks of treatment time occupied nearly 20% of the median overall survival for patients in the RT arm. As such, a protracted course of RT as used in the Canadian trials compress treatment length in an effort to provide improvement in quality of life while maintaining efficacy.

Chemotherapy alone in the elderly

Based on the success of TMZ in the European Organization for Research and Treatment of Cancer/National Cancer Institute of Canada (EORTC/NCIC) trial, several trials have been designed to evaluate the use of TMZ alone and compare it to radiation or supportive care alone. These studies, although heterogenous in design and in defined parameters, argue the use of TMZ alone for some elderly patients with High Grade Gliomas (HGG). Three randomized trials predominate the discussion of using TMZ alone in treatment of HGG in the elderly, all with the goal of maximizing treatment efficacy while simultaneously maximizing quality of life.

The first trial is the NOA-8 non-inferiority trial that enrolled 412 patients from 23 centers in Germany and Switzerland aged 65 and older with KPS scores of 60 or higher. Patients could have either GBM or AA histologies and were randomized to receive either 60 Gy adjuvant RT over 6-7 weeks or alternatively TMZ alone, given according to a one week on, one week off schedule with 100 mg/m^2 on days 1-7. Most patients in both arms underwent biopsy only (41% v. 37%, TMZ v. RT) prior to adjuvant treatment. After a minimum follow-up of 12 months, there was no significant difference in median event-free survival (EFS) between the TMZ and radiotherapy groups. Median overall survival was comparable in both groups at 8.6 months in the TMZ group and 9.6 months in the standard RT group ($p_{non-inferiority}$ = 0.033). Extent of

resection was identified as an independent prognostic factor for overall survival. The rate of adverse events was higher in the TMZ arm than the radiation alone arm. The most frequent grade 3-4 treatment related adverse events were hematologic cytopenias (76 events versus 7 events, TMZ v. RT), transaminitis (30 events vs 16, TMZ v. RT), infections (35 events v. 23 events TMZ v. RT) and thromboembolic events (24 events v. 8 events, TMZ v RT) [17].

The second and similarly designed Nordic multicenter trial randomized 291 patients aged 60 and older with GBM with ECOG PS 0-2 to one of three arms: RT of 60 Gy in 30 fractions over 6 week, TMZ alone administered orally at 200 mg/m^2 on days 1-5 every 28 days for six cycles or HF RT of 34 Gy in 10 fractions over two weeks. In the group receiving TMZ alone, median survival was significantly longer than the group receiving standard RT (8.3 months compared to 6.0 months, p = 0.01). The survival of the group receiving standard fractionated radiation was significantly less than the similar trial arm from the NOA trial, possibly due to poor treatment adherence (22% drop-out rate in 4 weeks for standard RT arm v. 14% drop-out in 4 weeks in the TMZ arm). Other important potential confounders included a delay in treatment with the median time of 46 days from surgery to start of standard radiotherapy, which was almost double the time compared to patients in the TMZ group [2]. By comparison, the median start date for radiotherapy in the NOA-8 trial was median 30 days after surgery [17]. Adverse events included neutropenia and thrombocytopenia in the TMZ treatment arm, which were similar to the NOA trial. Additionally, TMZ alone seemed to improve symptoms and function scores in several health-related QOLdomains when taken longitudinally through the study.

The French "ANOCEF" (Association des Neuro-Oncologue d'Expression Française) trial published by Gallego et al is the third trial evaluating TMZ alone as a treatment arm for HGG in the elderly and compared to historical control of best supportive care [22]. In this trial, 70 patients age 70 years and older with a (KPS) less than 70 (median 60) were treated with TMZ 150-200 mg/m^2. In the TMZ treatment arm up to 12 cycles of adjuvant TMZ was initiated within the first month after diagnostic biopsy or resection. Median progression free survival (PFS) was 16 weeks and overall sur-

vival (OS) 25 weeks. These results were favorable when compared to historical outcomes for best supportive care (OS range 12 to 16 weeks). This study also found that patients with O-methylguanine-DNA methyltransferase (MG-MT) promoter methylation had longer OS (31 versus 19 weeks), although MGMT data was present in only 44% of the patients studied. The median OS among patients with methylation was 31 compared with 18.7 weeks in patients with non-methylated tumors. This study demonstrated acceptable tolerance of TMZ in elderly patients with only few patients demonstrating neutropenia and thrombocytopenia (13% and 14% of patients respectively). Additionally, this study showed that the KPS improved in 23 patients (32.9%) after TMZ treatment with a median improvement of 20 points. The median duration of such improvement was 4 months. This study suggests an acceptable tolerance to TMZ in elderly patients with GBM and KPS less than 70 while simultaneously giving patients an improvement of functional status and an increase survival compared with supportive care alone, especially in patients with methylated MGMT promoter [18]. Overall, these studies promote the use of adjuvant TMZ in the elderly population, however they do not address the role of radiotherapy.

Combined adjuvant radiotherapy and chemotherapy

The treatment benefit for the use of both combined chemoradiation and/or sequential adjuvant chemotherapy after surgery in the elderly population has been evaluated in prior studies. Heterogeneity in the design of these studies makes them a challenge to interpret when making clinical decisions, however their outcomes should be considered.

One such Italian group enrolled 79 consecutive elderly patients over the age of 65 and KPS > 60 with GBM in a prospective clinical trial from 1993-2000. Patients underwent maximally safe resection of their tumors followed by either adjuvant involved-field radiation alone (59.4 Gy in 1.8-2.0 Gy fractions), radiotherapy followed by Procarbazine/CCNU/Vincristine "PCV" chemotherapy, or radiotherapy plus TMZ. Adjuvant chemotherapy was started 4 weeks after completion of radiotherapy. Median survival was 11.2 months for RT alone versus 12.7 with adjuvant PCV and 14.9 months with RT and

adjuvant TMZ. Toxicity was mild in the radiation alone group, with only 7% of patients developing mild signs of intra-cranial edema that resolved with medical therapies. In the group receiving RT followed by TMZ, toxicity included grade 3 thrombocytopenia in 1.7%, grade 2 thrombocytopenia in 4.3%, and leukopenia seen in 6% of all 114 cycles of chemotherapy. In light of the improved survival benefit, ease of administration and low toxicity the study authors concluded that TMZ should be the chemotherap agent of choice over PCV in elderly patients with good KPS undergoing combined-modality treatment [19].

A prospective, multicenter phase II Italian study by Minniti and colleagues was conducted to determine if the hypothetical quality of life improvement gained from hypofractionated RT could be coupled with the survival gains from concurrent and adjuvant temozolamide seen in the Stupp trial. 71 patients with newly diagnosed GBM who were 70 years and older and had a KPS score of 60 or higher underwent surgical resection. They then received focal RT with concomitant daily temozolamide followed by adjuvant temozolamide. RT consisted of 40 Gy in 15 fractions to a volume encompassing residual enhancing tumor on T1 MRI plus a variable margin of between 0.9-2.4 cm. RT was started within 4 weeks of surgery and was given with concomitant temozolamde at a dosage of 75 mg/m^2 for the duration of RT. Adjuvant temozolamide was started 4 weeks after RT ended and consisted of 150 mg/m^2 during the first cycle, increased to 200 mg/m^2 from the second cycle onwards. The majority of patients (61%) had a subtotal or partial tumor resection. The median OS was 12.4 months, median PFS was 6 months, and 1-year and 2-year OS rates were 58% and 20%, respectively. The authors also reviewed the secondary endpoint of toxicity and found no grade 3 thrombocytopenia during concomitant RT-TMZ; however 14% of patients had grade 3 or 4 thrombocytopenia during the adjuvant phase. Four patients experienced a reversible worsening of neurologic status during or immediately after concomitant RT and TMZ. Three more patients experienced neurologic deterioration after greater than 6 months out from completing RT [20]. A companion study was conducted to look at quality of life for patients in this study. Sixty-five patients completed a baseline questionnaire

Table 1. Pertinent studies of treatment for high grade gliomas in the elderly

Study	Age (years)	KPS	Radiation	Chemotherapy	Progression Free Survival	Overall Survival
Keime-Guibert et al, 2007	≥ 70 (Median 73)	≥ 70	50.4 Gy in 1.8 Gy fractions	—	14.9 weeks	29.1 weeks
Roa et al, 2004	≥ 60 (Mean 72)	≥ 50 (Median 70)	40 Gy in 15 fractions over 3 weeks	—		5.1 months
Wick et al, 2012 NOA-8 trial	≥ 65	≥ 60	60 Gy over 6 weeks	—	4.7 months	9.6 months
			—	100 mg/m² 1 week on and 1 week off	3.3 months	8.6 months
Malmstrom et al, 2012 Nordic trial	≥ 60		60 Gy over 6 weeks	—		6 months
			—	200 mg/m² Days 1-5 (28 day cycle) for 6 cycles		8.3 months
			34 Gy in 10 fractions over 2 weeks	—		7.5 months
Gallego et al, 2011 ANOCEF	≥ 70	< 70	—	150 mg/m² Days 1-5 (28 day cycle) for up to 12 cycles	16 weeks	25 weeks
Brandes et al, 2003	≥ 65 (Mean 69)	> 60 (Median 80)	59.4 Gy in 1.8-2.0 fractions	—	5.3 months	11.2 months
			59.4 Gy in 1.8-2.0 fractions	PCV*	6.9 months	12.7 months
			59.4 Gy in 1.8-2.0 fractions	150 mg/m² for 5 days every 28 days	10.7 months	14.9 months
Minniti et al, 2012	≥ 70 (Median 73)	> 60 (Median 70)	40 Gy in 15 fractions with concomitant TMZ**	150-200 mg/m²	6 months	12.4 months
Floyd et al, 2012	65-87 (Median 75.4)	> 70	40 Gy in 15 fractions with SRS boost of 15-22 Gy with concomitant TMZ**	150 mg/m² Days 1-5 (28 day cycle) for 1 year or until 28 cycles	11 months	13 months

*Lomustine 110 mg/m² Day 1, procarbazine 60 mg/m² on Days 8–21, and vincristine 1.4 mg/m² (maximum, 2 mg) on Days 8 and 29 were administered every 8 weeks. **Concomitant temozolomide is dosed at 75 mg/m² on days of radiation.

and had changes in 9 pre-selected domains determined by repeat questionnaire at 4 weeks post-RT and every 8 weeks thereafter until disease progression. There was an improvement in mean social functioning and cognitive functioning scores but a worsening in fatigue [21].

Significance of MGMT promoter methylation status

Retrospective data analysis of patients from the Stupp trial determined that the methylation status of the MGMT promoter predicts response to treatment. Patients with MGMT promoter methylation had statistically significant improvements in median OS, and 2- and 5-year OS rates compared to patients without the MGMT promoter methylation. This phenomenon has since been shown in many other trials including the previously mentioned NOA-8 trial where MGMT promoter status was associated with improved median EFS in the TMZ group (8.4 mo v 3.3 mo, methylated MGMT v unmethylated MGMT) [17], and in the Nordic trial which likewise found significantly longer survival in patients treated with TMZ who were MGMT methylated as compared to the unmethylated group (9.7 mo v 6.8 mo, methylated MGMT v. unmethylated MGMT) [2]. In the Minetti Italian phase II trial of surgery, hypofractionated RT with concurrent and adjuvant TMZ trial, multivariate analysis also showed that MGMT methylation status was a significant independent prognostic factor. Median OS was 15.8 months in patients with methylated GBMs versus 8.8 months in those with unmethylated GBMs. Overall, these studies argue that the efficacy of TMZ in patients with MGMT methylation outweighs potential toxicity. How this use of TMZ fits in with each patient's radiation course whether standard of care, HF RT or omitted remains unclear.

Role for EBRT + SRS

In recognition of the fact that 90% of GBM recurrences occur within 2 cm of the enhancing edge of the original tumor [22], the Radiation Therapy Oncology Group (RTOG) conducted a randomized trial comparing stereotactic radiosurgery (SRS) followed by standard RT with concurrent BCNU chemotherapy to standard RT with BCNU alone in patients with GBM. Though enrollment included patients aged 18 and up, 68% of the 97 patients in the standard RT arm were 50 years or older and 69% of 89 patients in the RT + SRS arm were 50 or older. In both arms, standard RT was given to a dose of 60 Gy in 2 Gy fractions. The first 23 fractions were to a treatment volume including enhancing tumor and surrounding edema on a pre-operative scan plus a 2-2.5 cm margin. The final 14 Gy was delivered to the enhancing tumor plus 2.5 cm. One week prior to starting RT, patients in the SRS plus RT arm received a volume dependent SRS treatment to the tumor per RTOG protocol 9005. SRS doses ranged from 15-24 Gy, and treatment could be delivered using either Gamma knife or linear-accelerator based radiosurgical technique. After median follow-up of 61 months, median survival was not statistically different, consisting of 13.5 months in the SRS group and 13.6 months in the standard arm. Although this study found no evidence to support the addition of SRS to standard RT for GBM, there remains interest in the use of SRS as a boost to HF therapy, particularly in the elderly population, where short course RT + SRS boost may approximate the results of standard fractionated RT while maintaining the benefits of a shorter overall treatment time [23]. To that end, Floyd et al, have published early results of a Phase II trial of HF RT followed by stereotactic boost both given with concurrent TMZ. 20 patients aged 65-87 with GBM and KPS > 70 were enrolled and treated with RT to 40 Gy in 15 fractions to the commonly used volume. Patients then received SRS boost using CyberKnife to deliver volume-dependent boost of between 15-22 Gy in 3 fractions to contrast enhancing tumor. Radiotherapy was given concurrent with TMZ and followed by adjuvant TMZ through one year or 28 cycles, which ever was longer. After median follow-up of 11 months, no increase in PFS or OS was seen when compared to historical data with a median PFS measuring 11 months and median OS measuring 13 months [24].

Conclusion

Pertinent studies of treatment for high grade gliomas in the elderly are summarized in **Table 1**. Despite the multiple clinical trials evaluating HGG treatment in the elderly, no single standard of care exists for this patient population. Six week RT with concurrent and adjuvant TMZ (The "Stupp Protocol"), standard course RT, HF RT, and TMZ monotherapy, can all be consid-

ered reasonable treatment options in elderly patients depending on how the trial data is interpreted. In clinical practice, MGMT promoter methylation status may be a useful marker to determine benefit from TMZ [2]. At our institution, if an older HGG patient presents with good KPS, he or she is treated with the standard of care "Stupp" regimen. If a patient has compromised KPS, MGMT methylation status is used to determine whether TMZ will be used for treatment both concurrently with radiation and/or as adjuvant cycles. Radiation course is also decided based on a patient's functional status and may be abbreviated with HF RT or omitted altogether if the patient is unable to tolerate.

Future directions of treatment will focus on specific tumor biology and markers including MGMT promoter methylation. The EORTC/NCIC Intergroup is presently conducting a randomized phase III trial for patients with newly diagnosed GBM aged 65 and older who will be assigned to receive either hypofractionated involved-field radiation alone (40 Gy in 15 fractions) versus the same radiotherapy plus concurrent and adjuvant temozolamide. Once accrual is met, this study may provide the most insight yet into the best treatment strategy for elderly patients with GBM in the modern era. Other groups are looking at the potential efficacy of bevacizumab (BVZ) in the elderly population. Collaborators from the University of Zurich in Germany are evaluating the efficacy of bevacizumab (Avastin [Genentech/Roche]) with RT compared to RT alone in a randomized trial of newly diagnosed GBM patients 65 and older (Avastin Plus Radiotherapy in Elderly Patients with Glioblastoma [ARTE]). A phase II trial in the US is evaluating the benefits on BVZ and TMZ together in patients with newly diagnosed GBM over the age of 70 [25]. Based on the Canadian trial, a shorter course of RT given in 3 weeks appears to be as effective as a standard course of a 6 week regimen. Investigators from the International Atomic Energy Agency (IAEA) are looking at the benefit of 40 Gy in 15 fractions over 3 weeks as used in the Canadian trial versus 25 Gy in 5 fractions given over a week in a international phase III clinical trial for patients over the age of 65 and KPS of 50 or above [6]. Ongoing clinical trials will help shed light on optimal strategies in the care of these patients. Overall, treating oncologists must weigh the efficacy of treatment while also maintaining a patient's quality of life. This balance is one clinicians struggle with for all patients, and is particularly highlighted in elderly patients with HGG.

Disclosure of conflict of interest

None to declare.

Address correspondence to: Dr. Samir V Sejpal, Department of Radiation Oncology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA. E-mail: ssejpal@nmff.org

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