Elderly Patients with Glioblastoma Multiforme Treated with Concurrent Temozolomide and Standard- versus Abbreviated-Course Radiotherapy

Christine N Chang-Halpenny, MD; Jekwon Yeh, MD; Winston W Lien, MD

Perm J 2015 Winter;19(1):15-20
http://dx.doi.org/10.7812/TPP/14-083

ABSTRACT

Context: Glioblastoma multiforme (GBM) is an aggressive neoplasm, with controversy regarding treatment in elderly patients.

Objective: To review outcomes of elderly patients aged ≥ 65 with newly diagnosed GBM treated with concurrent temozolomide and either standard-course radiotherapy (SRT) or abbreviated-course radiotherapy (ART).

Design: Retrospective review from 2003 to 2012.

Main Outcome Measure: Survival, comparing treatment regimens. One hundred patients received SRT (median dose = 60 Gy), and 29 received ART (median dose = 35 Gy). O6-methylguanine-DNA methyltransferase (MGMT) status was available for 26 SRT and 13 ART recipients.

Results: Median age was 70 years. Median follow-up was 11 months. At analysis, 3 patients were alive. Multivariate analysis of the entire cohort found SRT (hazard ratio [HR] = 0.421, p = 0.0001), Karnofsky Performance Score of 70 or higher (HR = 1.894, p = 0.0031), and more extensive surgery (HR = 0.466, p = 0.0023) were associated with longer survival time, but age was not. Median time to death with SRT was 13 months versus 5.4 months with ART, but the latter had worse prognostic factors, including lower Karnofsky Performance Scores, fewer gross total resections, and higher recursive partitioning analysis class. Recipients of SRT with methylated MGMT promoter had a trend toward longer survival compared with unmethylated MGMT (p = 0.06), but ART recipients had shorter survival with MGMT methylation (p = 0.02).

Conclusion: Elderly patients with multiple poor prognostic factors given ART had short survival times. Relative to other variables, MGMT status may not predict outcome for these patients.

INTRODUCTION

Glioblastoma multiforme (GBM) is a brain neoplasm with aggressive behavior and a 5-year overall survival less than 5%.[1] At present, all treatment is essentially palliative, with eventual progression of disease. Current standard of care includes concurrent temozolomide (TMZ) and radiation therapy (RT) to 60 Gy in 2-Gy daily fractions, followed by adjuvant TMZ therapy.[2-4] Optimal treatment of elderly patients is controversial because of their underrepresentation in early trials. This may be the result of multiple factors, including coexisting medical conditions and poor performance status. Studies before the TMZ era in elderly patients found improved survival with RT vs supportive care alone.[5] Also, standard-dose and lower-total-dose irradiation were shown to have equivalent survival outcomes in elderly patients.[6] A shorter course of RT may be more convenient for patients without being a detriment to survival.

Results of 2 recently published Phase 3 trials suggest that TMZ alone or RT alone may be good options in treating elderly patients with GBM and good Karnofsky Performance Scores, with similar outcomes from both arms.[7,8] Both trials found that elderly patients with O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation (mMGMT) had longer survival times than those with unmethylated MGMT (uMGMT) promoter when all were treated with TMZ alone.[7,8] Previously, MGMT methylation has been shown to be associated with statistically significantly longer survival in patients receiving TMZ treatment.[3,9] TMZ methylates DNA at multiple sites, including guanine at the O6 position, and unless repaired by a process with MGMT, the active drug leads to double-strand breaks. The efficacy of TMZ is thought to be related to MGMT methylation through increased drug sensitivity related to epigenetic gene silencing and enzyme inactivation. Despite this, it has not yet been widely incorporated into clinical practice (for prognosis or decision making).

Although these studies investigated outcomes from patients treated with single-modality TMZ or RT, the question remains whether concurrent TMZ with RT would be of further benefit to elderly patients. Results of existing studies looking at elderly patients given concurrent TMZ-RT suggest reasonable toxicities and a possible benefit of TMZ with RT; however, they are limited by either small numbers or lack of MGMT data,[10-16] or are contradictory, with Niyazi et al[17] finding that patients aged 70 years and older with lower Karnofsky Performance Scores might have worse outcomes if given TMZ. Results of a handful of studies also suggest that TMZ with an abbreviated course of RT or hypofractionated regimen may have similar outcomes as standard RT.[18-21] Our study presents a review of our institution's data of patients aged 65 years and older with newly diagnosed GBM who were treated with concurrent TMZ-RT, with standard-course RT

Christine N Chang-Halpenny, MD, is a Radiation Oncologist at the Sunset Medical Center in Los Angeles, CA. E-mail: christine.n.chang-halpenny@kp.org. **Jekwon Yeh, MD,** is a Radiation Oncologist at the Cancer Center of Irvine in CA. E-mail: jyeh.md22@ccoi.org. **Winston W Lien, MD,** is a Radiation Oncologist at the Sunset Medical Center in Los Angeles, CA. E-mail: winston.w.lien@kp.org.

(SRT) or abbreviated-course RT (ART). The latter typically is used for patients with worse prognostic factors. We also present MGMT data, available for a subset of our patients.

METHODS

Patients and Data Analysis

A retrospective review was conducted after obtaining permission from our institutional review board. We included patients aged 65 years or older treated with concurrent TMZ and RT for newly diagnosed GBM and treated at Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA. Patients' clinical presentation (symptoms, neurologic status, Karnofsky Performance Score status), tumor characteristics (maximum tumor dimension and focality), degree of resection (according to the operative report), treatment, and outcomes were noted. The Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis status was determined via chart review.[22,23] For patients aged 70 years and older, recursive partitioning analysis classification is limited to Classes IV, V, or VI, but Classes IV and V are differentiated only by working status. Because most of our patients were retirees, Classes IV and V were merged into 1 group for the purposes of the study. Survival time was calculated from date of tissue diagnosis to death (the latter via the US Social Security Death Index or the patient's medical record). We did not note progression because of the retrospective nature of the study and variable imaging times.

Statistical analysis was conducted using GraphPad Prism 6.0 (GraphPad Software Inc, La Jolla, CA) and SAS (SAS Institute Inc, Cary, NC). Variables included in statistical analysis were radiation course, recursive partitioning analysis class, Karnofsky Performance Score (≤ 70 or > 70), tumor focality, extent of resection, up-front bevacizumab administration, and age. Survival times and significance were calculated using Kaplan-Meier analysis with univariate log-rank test and multivariate analysis with Cox proportional hazards model.

Table 1. Characteristics of patients receiving standard-course radiation therapy (RT) and abbreviated-course RT[a]

Characteristic	Standard course RT (n = 100)	Abbreviated course RT (n = 29)
Median age, years (range)	69 (65-93)	75 (66-87)
Men	64	62
Women	36	38
Seizures	22	24
Headache	31	34
Vision changes	16	3
Motor deficits	28	45
Numbness	7	10
Altered mental status	38	41
RTOG RPA		
Classes IV, V	94	66
Class VI	6	35
Karnofsky Performance Score		
Median Score (range)	90 (50-100)	70 (30-90)
Tumor		
Maximum size, cm (range)	4.3 (1.2-8)	5 (2-8)
Unifocal	81	72
Multifocal	19	28
Treatment		
Biopsy	29	31
Subtotal resection	41	62
Gross total resection	30	7
Median RT dose, Gy (range)	60 (50.4-64.08)	35 (20-42)
Carmustine wafers	6	3.4 (1/29)
Concurrent bevacizumab	16	31
MGMT status		
Available (no.)	26 (26/100)	45 (13/29)
Unmethylated (no.)	73 (19/26)	54 (7/13)
Methylated (no.)	27 (7/26)	46 (6/13)

[a] Data are in percentage of patients unless indicated otherwise.
MGMT = O6-methylguanine-DNA methyltransferase; RTOG RPA = Radiation Therapy Oncology Group recursive partitioning analysis.

Treatment

All patients had histologically proven GBM via biopsy or subtotal resection or gross total resection. The extent of resection was decided by the operating neurosurgeon. Radiation therapy was delivered Monday through Friday using linear accelerators with an energy of 6 mV. Recipients of SRT received a median dose of 60 Gy in 2-Gy daily fractions. A planning computed tomographic scan was fused with magnetic resonance imaging, and depending on the individual case, the area of edema (determined by magnetic resonance imaging with fluid-attenuated inversion recovery) plus the surgical margin was treated to 60 Gy or to 46 Gy of radiation followed by field reduction to a smaller volume of contrast enhancement plus the margin to an additional 14 Gy, totaling 60 Gy for the smaller volume. Recipients of ART received a median dose of 35 Gy in 3.5-Gy daily fractions. Most patients were treated with 3-dimensional conformal RT (75%), with intensity-modulated RT, standard since about 2010. TMZ-based chemotherapy was given according to the trial by Stupp et al,[2,3] in terms of dose and timing. Patients also received additional systemic agents (bevacizumab or carmustine wafers) depending on physician preference, as detailed in Table 1.

RESULTS

All Patients

From 2003 to 2012, we identified 129 patients who were age 65 years or older with newly diagnosed, histologically proven GBM. Of these, 100 patients were treated with SRT and 29 patients with ART. Promoter hypermethylation data for MGMT, via methylation-specific polymerase chain reaction, was available for 30% of patients. Overall median age was 70 years (range = 65 to 93 years), and median follow-up time was 11 months (range = 1.7 to 71.8 months).

The most common presenting symptoms were altered mental status (38.8%), followed by headache and change in motor function (both 31.8%), seizures (22.5%), changes in vision (13.2%), and sensory changes (7.8%). Gross total resection was performed in 24.8% of patients; subtotal resection, in

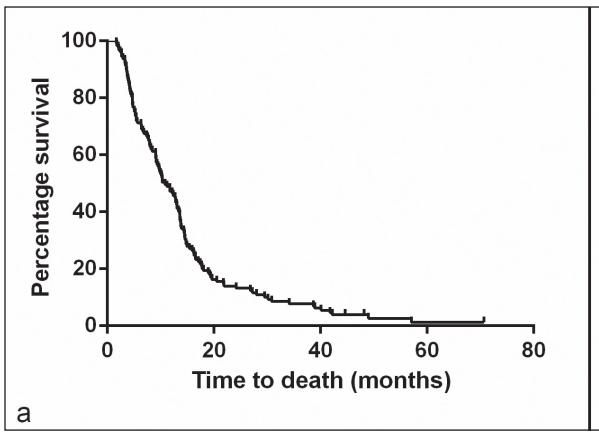

Figure 1a. Kaplan-Meier survival curves for all patients.

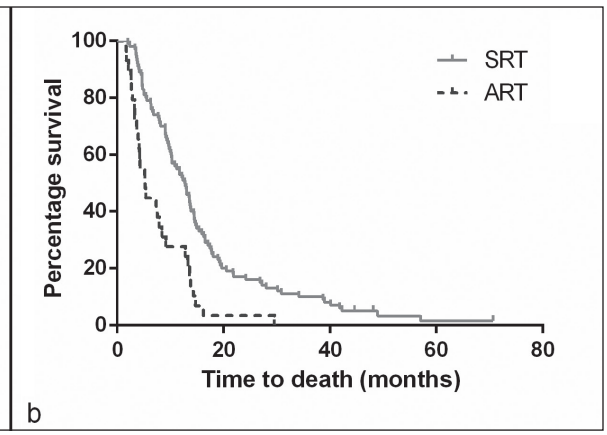

Figure 1b. Kaplan-Meier survival curves for patients treated with standard-course radiation therapy (SRT, solid line) or abbreviated-course radiation therapy (ART, dashed line).

45.7%; and biopsy only, in 29.5%. Median overall survival was 10.5 months (range = 1.7 to 57.9 months). By the time of retrospective analysis, only 3 patients were still alive (overall mortality of 98.4%, Figure 1), all having received SRT. As expected, the group that received ART had worse prognostic factors (see Abbreviated-Course Radiation Therapy section). Otherwise, the groups were relatively similar in clinical characteristics (Table 1).

Kaplan-Meier analysis with the log-rank test showed statistically significantly higher median survival time with SRT ($p < 0.0001$). In addition, the log-rank test showed higher median survival times for recursive partitioning analysis Class IV/V compared with Class VI ($p = 0.0413$), as well as for those with Karnofsky Performance Scores above 70 ($p = 0.0013$), those who underwent resection rather than biopsy ($p = 0.0007$), and those patients not given bevacizumab (with TMZ) as initial treatment ($p = 0.0033$). The MGMT status was not significant on log-rank for the entire cohort, but it became a significant factor when tested separately in the SRT and ART groups. When these variables, as well as age, were included in multivariate analysis, only RT course (SRT hazard ratio [HR] = 0.421, $p = 0.0001$), Karnofsky Performance Score (≤ 70 HR = 1.894, $p = 0.0031$), and resection rather than biopsy (gross total resection: HR = 0.466, $p = 0.0023$; subtotal resection: HR = 0.455, $p = 0.0003$) were significant according to the Cox proportional hazards model. Age was not a significant factor. The median survival time for patients with Karnofsky Performance Scores above 70 was 13 months vs 7.4 months for those with scores of 70 or below. The median survival time for patients who underwent biopsy was 6.13 months vs 13.3 months for those who underwent subtotal resection and 14 months for patients who underwent gross total resection. More complete data regarding RT course and MGMT data are reported separately as below.

Standard-Course Radiation Therapy

The median age of patients treated with SRT was 69 years (range = 65 to 93 years). Most patients received 60 Gy in 30 fractions (range = 50.4 to 64.08 Gy). All but 1 patient received partial brain irradiation. In addition to TMZ, 16% received bevacizumab as part of initial therapy, and 6 patients had carmustine wafers implanted at the time of surgery. The median time to death was 13 months (range = 2 to 72 months). Salvage (rescue) chemotherapy was given to 56% of SRT recipients. Four patients received repeated irradiation to treat a recurrence. The median time from salvage therapy to death for SRT recipients was 7.3 months (range = 0.3 to 30 months). Overall survival at 1 year was 54% and at 2 years was 17%. See Table 2 for outcomes data comparing SRT and ART.

On univariate analysis, the median survival time was significantly longer for patients not given bevacizumab as part of initial treatment ($p = 0.0216$) and for patients who received gross total resection or subtotal resection vs biopsy ($p = 0.0024$). On multivariate analysis, both bevacizumab (HR = 1.896, $p = 0.0268$) and degree of resection (gross total resection: HR = 0.451, $p = 0.003$; subtotal resection: HR = 0.481, $p = 0.0033$) remained significant variables affecting

Table 2. Patient salvage treatment and outcomes by radiation therapy (RT) course

Salvage therapy	Standard-course RT (n = 100)	Abbreviated-course RT (n = 29)
Received repeated irradiation, %	4	0
Received chemotherapy, %	56	24
Median months from diagnosis to salvage therapy (range)	9.5 (2.3-60.7)	7.2 (2.3-21.8)
Median months after salvage therapy to death (range)	7.3 (0.3-30)	6.6 (1.4-9.7)
Outcomes		
Median follow-up, months (range)	13 (2-71.8)	5.4 (1.7-29.9)
Overall mortality, %	97	100
Median months from surgery to death (range)	13 (2-71)	5.4 (1.7-30)
Overall survival at 1 year, %	54	8
Overall survival at 2 years, %	17	1

survival times. Of note, in the SRT cohort, those patients given bevacizumab had significantly worse Karnofsky Performance Scores (≤ 70 for 12 patients and > 70 for 6 patients, p = 0.0733), which may be a confounding factor.

Abbreviated-Course Radiation Therapy

The median age for patients treated with ART was 75 years (range = 66 to 87 years). Compared with patients treated with SRT, recipients of ART had lower Karnofsky Performance Scores (≤ 70 for 51% vs > 70 for 18%, p = 0.0002), fewer gross total resections (7% vs 30%, p = 0.011) and higher recursive partitioning analysis (Class VI/V 87.6% vs Class V 12.4%, p = 0.0003). Most patients received 35 Gy in 10 daily fractions (range = 20 to 42 Gy). Field of treatment consisted of partial-brain irradiation for 59% of patients, whereas 41% received whole-brain irradiation. The median time to death was 5.4 months (range = 1.7 to 30 months). More ART recipients received concurrent bevacizumab as first-line treatment (16% vs 31%, p = 0.07) compared with those in the SRT group. One patient had carmustine wafers implanted. Only 24% received salvage chemotherapy, and none received repeated irradiation. Median time from salvage to death for ART patients was 6.6 months (range = 1.4 to 9.7 months). Overall survival at 1 year was 8% and at 2 years was merely 1%.

By univariate analysis, median survival time was significantly longer for patients with Karnofsky Performance Scores above 70 (p = 0.0073), uMGMT promoter (p = 0.021), and unifocal disease (p = 0.0026). The extent of resection and bevacizumab treatment were not significant variables, in contrast to the SRT group. After multivariate analysis, only Karnofsky Performance Score (≤ 70: HR = 3.312, p = 0.0074) and tumor focality (multifocality: HR = 4.259, p = 0.0031) were significant.

06-Methylguanine-DNA Methyltransferase Promotor Status

Data on MGMT were available for 39 patients (26 SRT and 13 ART). Log-rank analysis of MGMT status for all patients did not show significantly different survival times (p = 0.5412). However, methylation status was significantly associated with outcomes for patients when data were analyzed separated by the RT course given. For patients whose MGMT status was known, the SRT group had more gross total resections compared with those in the ART group (p = 0.0272), more cases of recursive partitioning analysis Class VI (p = 0.0620), and more patients treated with bevacizumab up front (p = 0.0597). Median age was similar, and Karnofsky Performance Score was slightly lower (median Karnofsky Performance Score = 90 for ART vs 80 for SRT). Of the 26 SRT patients for whom MGMT data were known, 7 had mMGMT status and 19 had uMGMT status. Patients given SRT with mMGMT status had a trend toward longer survival times compared with those with uMGMT status: 28.4 months (range = 3.4 to 57.9 months) vs 10.3 months (range = 3.5 to 49.7 months, p = 0.0602, Figure 2). Median age was slightly higher in the SRT group for patients with mMGMT status than for those with uMGMT status (75 vs 69 years); otherwise, there were no significant differences by recursive partitioning analysis class, Karnofsky Performance Score, surgery type, or radiation dose.

Of the 13 ART patients with MGMT data, 6 had methylated and 7 had unmethylated status. Paradoxically, patients treated with ART actually had significantly shorter survival if promoter methylation was present. Time to death for patients with mMGMT status was 3 months (range = 1.7 to 8.6 months) vs 14.5 months (range = 2.2 to 14.5 months) for those with uMGMT (p = 0.021). In the ART group, patients with mMGMT status did not differ significantly from those with uMGMT status in potential prognostic factors.

DISCUSSION

Recent large randomized trials have investigated outcomes for elderly patients with newly diagnosed GBM treated with TMZ alone or RT alone, but not combined. Current guidelines for GBM management from the National Comprehensive Cancer Network have treatment arms stratified by performance status but have a range of options for patients over age 70 years who have Karnofsky Performance Scores of 70 or higher; these options include either concurrent

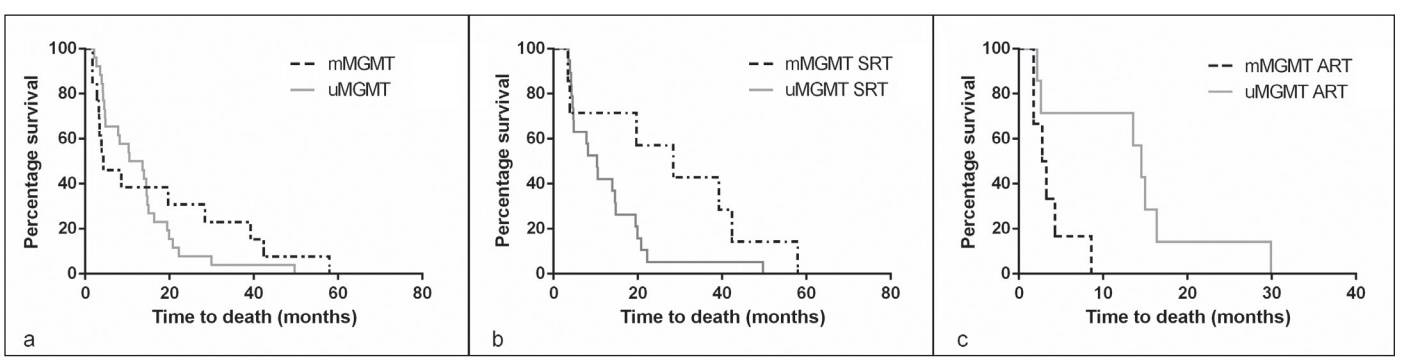

Figure 2a. Kaplan-Meier survival curves for patients with mMGMT (dashed line) vs uMGMT (solid line) promoter status.

Figure 2b. Kaplan-Meier survival curves for the subset of patients given SRT, mMGMT (dashed line) vs uMGMT (solid line) promoter status.

Figure 2c. Kaplan-Meier survival curves for patients given ART, mMGMT (dashed line) vs uMGMT (solid line) promoter status.

ART = abbreviated-course radiation therapy; mMGMT = methylated 06-methylguanine-DMA methyltransferase; SRT = standard-course radiation therapy; uMGMT = unmethylated 06-methylguanine-DMA methyltransferase.

treatment with TMZ-RT, hypofractionated RT alone, or TMZ therapy alone (if MGMT promoter is methylated).[24] Barker et al[11] looked at 291 patients aged 65 years and older who were treated with RT with or without chemotherapy and found that 2-year overall survival was significantly improved with TMZ: 14% vs 41%. Findings of other retrospective studies of elderly patients given combined-modality therapy suggest good tolerance of treatment.[11,12, 14,16]

According to our study of elderly patients with a range of Karnofsky Performance Scores, concurrent therapy with TMZ and standard-dose RT appeared to offer reasonable survival outcomes, with a median survival time of 13 months. Patients with multiple poor prognostic factors given ART had shorter survival times, with a median survival of 5.4 months. Multivariate analysis of prognostic factors suggested that SRT, Karnofsky Performance Score above 70, and more extensive resection are associated with better survival outcomes. For patients who received SRT, treatment with bevacizumab was associated with a shorter time to death, possibly confounded by SRT recipients given bevacizumab having lower Karnofsky Performance Scores to begin with. In both RTOG0825 and AVAglio, the addition of bevacizumab to treatment with TMZ and radiation found no significant difference in the duration of overall survival between bevacizumab and placebo, although progression free survival was improved with bevacizumab in the latter study.[25,26] Bevacizumab was not a significant variable on multivariate survival analysis for the entire cohort but may be a relevant area of study to further investigate its impact on older patients with GBM. Our study is limited by its retrospective nature, treatment by multiple providers, and the small number of patients for whom MGMT data are available.

Before TMZ was introduced, an abbreviated course of RT with a smaller dose of total radiation was suggested as treatment of GBM in elderly patients. Keime-Guibert[5] found that compared with supportive care alone, RT (50 Gy) modestly improved survival without reducing quality of life or cognition in elderly patients with high-grade gliomas and good Karnofsky Performance Scores. Roa et al[6] looked at elderly patients with Karnofsky Performance Scores of 50 or higher given a standard course of RT (60 Gy in 30 fractions) vs short-course irradiation (40 Gy in 15 fractions) and found decreased corticosteroid use and no significant difference in survival. In the trial by Stupp et al,[2,3] 30% of patients were age 60 to 70 years. In this subset of patients, median survival was similar to or slightly better for patients receiving RT alone vs chemoradiation therapy, although patients treated with TMZ had better overall survival over time because of a small subset of surviving patients. In the 2 largest Phase 3 trials focusing specifically on elderly patients (age 65 years or older), single-modality TMZ and RT each appears equally efficacious. The German Cancer Society Neuro-Oncology Working Group[7] found that dose-dense TMZ was not inferior to standard-dose RT, and health-related quality-of-life surveys were similar for both groups. The Nordic Clinic Brain Tumour Study group[8] looked at single-modality treatment with TMZ, standard-dose RT, or hypofractionated RT regimen. TMZ treatment alone had significantly better survival outcomes compared with standard RT but was equal to treatment with hypofractionated radiation. There was a trend for patients over age 70 years to have improved survival with TMZ treatment alone. In both studies, patients with mMGMT (vs uMGMT) promoter who were treated with TMZ had significantly improved survival. Given concerns about the ability of elderly patients to tolerate concurrent treatment, neither study looked at concurrent chemoradiation therapy and thus did not provide data on how methylation status affects patients given both TMZ and RT.

In our study, mMGMT status appeared beneficial for patients treated with SRT, although it probably did not reach statistical significance because of small numbers of patients. Interestingly, this was not true for patients treated with ART, in which patients with uMGMT status actually had better survival rates. It seems unlikely that methylation would be related to worse prognosis in these patients; rather, it is more likely that given the multiple poor prognostic factors and lower radiation dose in these patients, MGMT status may be less predictive compared with other prognostic factors when concurrent treatment with TMZ and RT is given. When we compared the two groups that had MGMT data, ART recipients had significantly fewer gross total resections, and there were more patients with recursive partitioning analysis Class VI, although this was not statistically significant.

Given the length of standard-dose RT, hypofractionation or an abbreviated course of RT is attractive for patient convenience and comfort, possibly with as few as 6 fractions of treatment.[27] Pilot and Phase 2 studies looking at hypofractionated courses of RT with TMZ have typically excluded elderly patients, but they show similar outcomes compared with SRT.[27-30] Hypofractionation studies that included elderly patients lack MGMT data but suggest similar outcomes with hypofractionated courses compared with standard RT.[18,19,31] Further studies on hypofractionation and concurrent and adjuvant TMZ therapy in elderly patients with good prognostic factors will, we hope, shed more light on the interplay of MGMT status and concurrent treatment for this subset of patients.

CONCLUSION

In our study, patients aged 65 years and older with newly diagnosed GBM had good outcomes when treated with SRT and concurrent TMZ, whereas patients with poor prognostic factors treated with ART and TMZ had shorter survival times. Methylated MGMT promoter status trended toward longer survival in SRT recipients, but may not be as useful in predicting outcomes for patients with worse prognostic factors treated with ART. Further investigation of the effect of bevacizumab on older patients with GBM is warranted. In the future, stratifying patients by MGMT status, as well as prognostic factors, and adapting treatment (with consideration of hypofractionated radiation regimen) on the basis of these factors would probably offer patients a better balance of treatment while minimizing toxicity. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgments

We would like to thank Richard M Green, MD, for his assistance.

Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance

References

1. Central Brain Tumor Registry of the United States (CBTRUS). CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2004-2008. Hinsdale, IL: Central Brain Tumor Registry of the United States; 2012 Feb [revised 2012 Mar 23]. p 1-58.
2. Stupp R, Mason WP, van den Bent MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005 Mar 10;352(10):987-96. DOI: http://dx.doi.org/10.1056/NEJMoa043330.
3. Stupp R, Hegi ME, Mason WP, et al; European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups; National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009 May;10(5):459-66. DOI: http://dx.doi.org/10.1016/S1470-2045(09)70025-7.
4. Athanassiou H, Synodinou M, Maragoudakis E, et al. Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. J Clin Oncol 2005 Apr 1;23(10):2372-7. DOI: http://dx.doi.org/10.1200/JCO.2005.00.331.
5. Keime-Guibert F, Chinot O, Taillandier L, et al; Association of French-Speaking Neuro-Oncologists. Radiotherapy for glioblastoma in the elderly. N Engl J Med 2007 Apr 12;356(15):1527-35. DOI: http://dx.doi.org/10.1056/NEJMoa065901.
6. Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol 2004 May 1;22(9):1583-8. DOI: http://dx.doi.org/10.1200/JCO.2004.06.082.
7. Wick W, Platten M, Meisner C, et al; NOA-08 Study Group of Neuro-oncology Working Group (NOA) of German Cancer Society. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol 2012 Jul;13(7):707-15. DOI: http://dx.doi.org/10.1016/S1470-2045(12)70164-X.
8. Malmström A, Grønberg BH, Marosi C, et al; Nordic Clinical Brain Tumour Study Group (NCBTSG). Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol 2012 Sep;13(9):916-26. DOI: http://dx.doi.org/10.1016/S1470-2045(12)70265-6.
9. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005 Mar 10;352(10):997-1003. DOI: http://dx.doi.org/10.1056/NEJMoa043331.
10. Laperriere N, Weller M, Stupp R, et al. Optimal management of elderly patients with glioblastoma. Can Treat Rev 2013 Jun;39(4):350-7. DOI: http://dx.doi.org/10.1016/j.ctrv.2012.05.008.
11. Barker CA, Chang M, Chou JF, et al. Radiotherapy and concomitant temozolomide may improve survival of elderly patients with glioblastoma. J Neurooncol 2012 Sep;109(2):391-7. DOI: http://dx.doi.org/10.1007/s11060-012-0906-4.
12. Hashem S, Salem A, Al-Rashdan A, et al. Radiotherapy with concurrent or sequential temozolomide in elderly patients with glioblastoma multiforme. J Med Imaging Radiat Oncol 2012 Apr;56(2):204-10. DOI: http://dx.doi.org/10.1111/j.1754-9485.2011.02325.x.
13. Brandes AA, Franceschi E, Tosoni A, et al. Temozolomide concomitant and adjuvant to radiotherapy in elderly patients with glioblastoma: correlation with MGMT promoter methylation status. Cancer 2009 Aug 1;115(15):3512-8. DOI: http://dx.doi.org/10.1002/cncr.24406.
14. Kimple RJ, Grabowski S, Papez M, Collichio F, Ewend MG, Morris DE. Concurrent temozolomide and radiation, a reasonable option for elderly patients with glioblastoma multiforme? Am J Clin Oncol 2010 Jun;33(3):265-70. DOI: http://dx.doi.org/10.1097/COC.0b013e3181a76a24.
15. Sijben AE, McIntyre JB, Roldán GB, et al. Toxicity from chemoradiotherapy in older patients with glioblastoma multiforme. J Neurooncol 2008 Aug;89(1):97-103. DOI: http://dx.doi.org/10.1007/s11060-008-9593-6.
16. Iwamoto FM, Cooper AR, Reiner AS, Nayak L, Abrey LE. Glioblastoma in the elderly. Cancer 2009 Aug 15;115(16):3758-66. DOI: http://dx.doi.org/10.1002/cncr.24413.
17. Niyazi M, Schwarz SB, Suchorska B, Belka C. Radiotherapy with and without temozolomide in elderly patients with glioblastoma. Strahlenther Onkol 2012 Feb;188(2):154-9. DOI: http://dx.doi.org/10.1007/s00066-011-0026-7.
18. Floyd SR, Kasper EM, Uhlmann EJ, Fonkem E, Wong ET, Mahadevan A. Hypofractionated radiotherapy and stereotactic boost with concurrent and adjuvant temozolomide for glioblastoma in good performance status elderly patients—early results of a phase II trial. Front Oncol 2012 Oct 16;2:122. DOI: http://dx.doi.org/10.3389/fonc.2012.00122.
19. Cao JQ, Fisher BJ, Bauman GS, Megyesi JF, Watling CJ, Macdonald DR. Hypofractionated radiotherapy with or without concurrent temozolomide in elderly patients with glioblastoma multiforme: a review of ten-year single institutional experience. J Neurooncol 2012 Apr;107(2):395-405. DOI: http://dx.doi.org/10.1007/s11060-011-0766-3.
20. Minniti G, Lanzetta G, Scaringi C, et al. Phase II study of short-course radiotherapy plus concomitant and adjuvant temozolomide in elderly patients with glioblastoma. Int J Radiat Oncol Biol Phys 2012 May 1;83(1):93-9. DOI: http://dx.doi.org/10.1016/j.ijrobp.2011.06.1992.
21. Reyngold M, Lassman A, Chan TA, Yamada Y, Gutin PH, Beal K. Abbreviated course of radiation therapy with concurrent temozolomide for high-grade glioma in patients of advanced age or poor functional status. J Neurooncol 2012 Dec;110(3):369-74. DOI: http://dx.doi.org/10.1007/s11060-012-0972-7.
22. Curran WJ Jr, Scott CB, Horton J, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst 1993 May 5;85(9):704-10. DOI: http://dx.doi.org/10.1093/jnci/85.9.704.
23. Scott CB, Scarantino C, Urtasun R, et al. Validation and predictive power of Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis classes for malignant glioma patients: a report using RTOG 90-06. Int J Radiat Oncol Biol Phys 1998 Jan 1;40(1):51-5. DOI: http://dx.doi.org/10.1016/S0360-3016(97)85345-X.
24. Brem SS, Bierman PJ, Brem H, et al; National Comprehensive Cancer Network. Central nervous system cancers. J Natl Compr Canc Netw 2011 Apr;9(4):352-400.
25. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. New Eng J Med 2014 Feb 20;370(8):699-708. DOI: http://dx.doi.org/10.1056/NEJMoa1308573
26. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. New Eng J Med 2014 Feb 20;370(8):709-22. DOI: http://dx.doi.org/10.1056/NEJMoa1308345.
27. Reddy K, Damek D, Gaspar LE, et al. Phase II trial of hypofractionated IMRT with temozolomide for patients with newly diagnosed glioblastoma multiforme. Int J Radiat Oncol Biol Phys 2012 Nov 1;84(3):655-60. DOI: http://dx.doi.org/10.1016/j.ijrobp.2012.01.035.
28. Floyd NS, Woo SY, Teh BS, et al. Hypofractionated intensity-modulated radiotherapy for primary glioblastoma multiforme. Int J Radiat Oncol Biol Phys 2004 Mar 1;58(3):721-6. DOI: http://dx.doi.org/10.1016/S0360-3016(03)01623-7.
29. Panet-Raymond V, Souhami L, Roberge D, et al. Accelerated hypofractionated intensity-modulated radiotherapy with concurrent and adjuvant temozolomide for patients with glioblastoma multiforme: a safety and efficacy analysis. Int J Radiat Oncol Biol Phys 2009 Feb 1;73(2):473-8. DOI: http://dx.doi.org/10.1016/j.ijrobp.2008.04.030.
30. Sultanem K, Patrocinio H, Lambert C, et al. The use of hypofractionated intensity-modulated irradiation in the treatment of glioblastoma multiforme: preliminary results of a prospective trial. Int J Radiat Oncol Biol Phys 2004 Jan 1;58(1):247-52. DOI: http://dx.doi.org/10.1016/S0360-3016(03)00819-8.
31. Minniti G, De Sanctis V, Muni R, et al. Hypofractionated radiotherapy followed by adjuvant chemotherapy with temozolomide in elderly patients with glioblastoma. J Neurooncol 2009 Jan;91(1):95-100. DOI: http://dx.doi.org/10.1007/s11060-008-9689-z.