Glioblastoma in the Elderly

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Abstract There is no generally agreed upon standard of care treatment for elderly patients (age ≥70 years) with glioblastoma (GBM). Treatment options range from supportive care only, radiation therapy (RT) only (most often given in a shortened hypofractionated schedule), temozolomide (TMZ) chemotherapy only, and the combination RT + TMZ, followed by post-RT TMZ as is the current standard of care for younger good performance patients with newly diagnosed GBM.

Keyword Glioblastoma · Elderly patients · Hypofractionated radiotherapy · Temozolomide

Contents

1 Introduction

The recently published randomized European Organization for Research and Treatment of Cancer and National Cancer Institute of Canada trial (EORTC/NCIC) substantially altered the algorithm for initial treatment of glioblastoma (GBM) [1]. This study of 573 patients demonstrated a statistically significant benefit (as determined by a 2.5 month improvement in median overall survival [mOS] when

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Table 1 Radiation therapy oncology group recursive partitioning classification system

Class^	Median overall survival (months)	2-year survival (%)
1	58	76
2	37	68
3*	18	35
4*	11	15
5*	9	6
6*	4.5	4

Legend ^Class defined by age, performance status, histology, neurological function and duration of symptoms
*Glioblastoma containing classes

Table 2 Hazard ration by age group in the EORTC/NCIC trial

Age, years (number of patients)	Hazard ratio	*P* value
<50 (171)	0.5	0.001
50–60 (220)	0.63	<0.05
61–65 (*)	0.72	0.096
66–71 (*)	0.8	0.34

*Age 61–71 years total number 173

compared to RT only) for chemotherapy (temozolomide [TMZ] given concurrently with radiotherapy [RT], followed by 6 monthly cycles of TMZ) in the initial treatment of good performance patients (Eastern Cooperative Oncology Group [ECOG] performance 0–2) with GBM. Notably, however, the study design excluded patients ≥70 years of age, a group of patients constituting >25 % of all newly diagnosed GBM [2–4]. Patients over the age of 70 years are most commonly defined as the elderly, though some definitions include patients aged 65 years and older. In a recent analysis of the EORTC/NCIC trial study, population stratified by the Radiation Therapy Oncology Group Recursive Partitioning Analysis (RTOG RPA) Class, benefit of RT + concomitant and adjuvant TMZ (RT + TMZ) was seen only in Class 3 and 4 patients (Table 1) [5]. In that more than 50 % of all elderly patients with GBM are characterized as RTOG RPA Class 5 or 6, RT only until recently was the standard treatment notwithstanding modest survival results [6, 7]. In that patients over the age of 70 years were not included in the landmark EORTC/NCIC trial, the question of the applicability of this regimen to patients over the age of 70 remains controversial. The utility of the EORTC/NCIC regimen of radiotherapy and concurrent and adjuvant TMZ was never well-defined for older patients with GBM and as seen in unpublished data from the EORTC Data Center in Table 2 (personal communication from Dr. James Perry), little benefit of this treatment strategy is apparent in patients >65 years of age. Currently, there are several treatment approaches to this demographically enlarging elderly patient population (Table 3). The diversity of treatments reflects both the limited prospective clinical trials in this patient population as well as a belief that standard of care (SOC) RT + TMZ followed by TMZ is of benefit, particularly in physiologically fit elderly patients with good performance [8–11].

Table 3 Treatment options for newly diagnosed elderly patients with glioblastoma

Treatment	Treatment parameters	Indication	Evidence
Radiation therapy only	40 Gy in 15 fractions	If MGMT methylation status not known or unmethylated	Evidenced-based
Temozolomide monotherapy	150–200 mg/m2/day x5 days every 4 weeks	If *MGMT* promoter methylation is present	Evidenced-based
Best supportive care		Impaired performance status unable to care for oneself	Not evidenced-based
Combination therapy	Standard protocol of RT (60 Gy in 30 fractions) with concurrent TMZ followed by 6 cycles of postradiotherapy TMZ	Patients with good performance status (KPS > 60)	Not evidenced-based
Clinical trial	Standard of care (RT + TMZ followed by TMZ) with an investigational agent	Patients with a good performance status (KPS > 60) and having undergone tumor resection (for tissue molecular correlates)	Investigational therapy

Legend *MGMT* Methylguanine-methytransferase, *KPS* Karnofsky performance status, *RT* Radiotherapy, *TMZ* Temozolomide, *Gy* Gray

Age is recognized as the most important prognostic factor for survival in GBM and survival declines after age 50 (a primary node point identified in the RTOG RPA classification system) [12]. Furthermore, there is a near linear decline in survival in patients with GBM greater than 50 years of age [3–5, 8]. Population-based studies of patients with newly diagnosed GBM show a mOS of 6 months in elderly patients, which is significantly lower than in younger patients [3, 5–7].

In addition to age, performance status (PS) is considered the second most relevant prognostic factor for survival in patients with GBM. Similar to patients >70 years of age, patients with markedly diminished or impoverished PS defined as an ECOG PS > 2 or a KPS < 60 have a mOS of 6 months or less. Because performance is so strongly correlated with survival, all current and most recent trials of newly diagnosed GBM only include patients with good performance status as defined by an ECOG performance score of 0–2 or a Karnofsky performance status of >60. These levels of performance imply independence in activities of daily living.

Two other relevant prognostic factors that are germane to elderly patients with GBM include tumor content of the DNA damage repair enzyme, methylguanine methyltransferase (*MGMT*), and the tumor mutational status of the isocitrate dehydrogenase 1 (*IDH1*) enzyme [13–17]. Patients with low tumor content of *MGMT*, a result of epigenetic silencing of the *MGMT* gene by promoter methylation, results in tumors with increased susceptibility to alkylator chemotherapy-induced injury. In elderly patients, the incidence of *MGMT* promoter methylated tumors is

either higher (50 % as assessed by the German Glioma Network) or similar to that seen in younger adult patients (30–40 %) suggesting either no age dependence of *MGMT* methylation or possibly an increase with age [18–20]. Regardless *MGMT* promoter methylation status does not appear to adversely influence outcome in elderly patients with GBM. By contrast, *IDH1* mutated gliomas currently defined as so-called secondary GBM, that is a GBM that arises from a lower grade glioma, have been demonstrated to have a more favorable outcome irrespective of treatment than the far more common (>90 %) primary GBM that arise de novo. The incidence of secondary GBM, however, decreases with age and, in contrast to *MGMT* promoter methylation, *IDH1* mutations are age dependent and only rarely manifest in GBM of elderly patients (<2 %) [21]. The rarity of *IDH1* mutated secondary GBM in the elderly may in part contribute to the above-mentioned poor overall survival.

Germane to treatment of elderly patients with GBM, geriatric oncologists recognize three categories of elderly patients based upon performance status, medical comorbidities, and age [22]. Frail elderly patients are defined by age >85 years (a category considered the oldest old), dependence in one or more activities of daily living, one or more medical comorbidities and one or more geriatric syndromes (defined as delirium, dementia, depression, osteoporosis, incontinence, falls, or failure to thrive). Physiologically, young elderly patients (as assessed by a geriatric scale) are defined by age <80 years, independence in activities of living, minimal to no medical comorbidities and no geriatric syndrome. The majority of clinical trials discussed below primarily relate to this category of elderly patient. The last category of elderly patients is those with a compromised PS that are dependent upon others in most or all activities of daily living. This category of elderly as well as younger patients with compromised PS is nearly always excluded from clinical trials due very limited survival.

2 Treatment

Several population-based studies document elderly patients with GBM receive less therapy than younger patients [3, 6, 7, 11, 23–25]. Of note the majority of published data on patterns of care in the elderly with GBM are derived before TMZ became available.

A SEER database analysis of 4,137 patients >65 years of age who were treated between 1994 and 2002 demonstrated that advancing age was associated with decreased use of resection, RT and chemotherapy, and with a diminished survival (mOS 4 months) [10]. A second SEER database analysis on 2,836 patients over the age of 70 showed that 86 % of patients received some form of treatment, but that only 46 % of patients underwent both surgery and RT [11]. In addition, another study reported that the rate of treatment with supportive care only increased with age [6]. A reason posited for diminished care in the elderly was the concern for increased toxicity from treatment with increasing age, patient preference, and the treating physician's perceived treatment nihilism.

Until recently, there was a paucity of randomized clinical trials for the elderly GBM patient population and consequently the most appropriate treatment for this large cohort of patients with newly diagnosed GBM was ill-defined and controversial (Table 4). Two previous randomized studies in elderly GBM patients demonstrated that involved field fractionated radiotherapy (RT50: 50 Gy in 28 fractions) is superior to supportive care only (median survival 7 vs. 4 months) and that conventional fractioned RT (sdRT; total dose 60 Gy in 30 fractions) is comparable to hypofractionated RT (hypoRT; 40 Gy in 15 fractions) [6, 7]. These trials provided evidence to commend in elderly patients with GBM and deemed candidates for treatment that hypoRT should serve as the standard of care for this subpopulation. Several subsequent retrospective studies suggested an alternative treatment that is standard dose TMZ (sdTMZ) with deferred RT, however, these studies constituted low level of evidence [26, 27].

A recent prospective randomized German study (NOA-08 study) compared up-front TMZ in a dose-dense regimen (ddTMZ is given at 100 mg/m^2/day for 7 consecutive days every 14 days) versus conventional fractioned RT (RT60: 60 Gy in 30 fractions) to elderly patients with high-grade glioma [HGG] (defined as age >65 years, KPS ≥ 60, and tumor histology GBM or anaplastic astrocytoma) {median survival 8.6 months vs. 9.6 months} [18]. The primary endpoint was overall survival and the trial design was that of a noninferiority endpoint. Median overall survival in the ddTMZ arm was 8.6 months versus 9.6 months in the sdRT arm demonstrating noninferiority between these two treatment regimens. As a consequence of this study, an evidence-based conclusion would be that TMZ may be administered as an alternative to elderly patients with GBM as opposed to sdRT. What remains unclear notwithstanding the above-mentioned three randomized trials is how to treat elderly patients with GBM that have an impoverished performance, a not uncommon situation that accounted in part for the reduced number of patients enrolled in the NOA-08 trial. Of 584 patients screened for NOA-08, only 373 patients were ultimately treated per protocol, the 209 patients [36 %] deemed ineligible were primarily due to poor PS. In addition, whether the use of ddTMZ as used in the NOA-08 trial is superior compared to the standard 5-day TMZ regimen (sdTMZ) is unclear. The recently completed Radiation Therapy Oncology Group study, RTOG 0525 in patients with newly diagnosed GBM demonstrated no survival benefit to post-RT ddTMZ [19]. Further, the recently completed Medical Research Council trial of chemotherapy for chemotherapy naïve HGG in first relapse after treatment with surgery and RT showed no benefit to ddTMZ compared to sdTMZ [28]. Dose dense TMZ as acknowledged by the NOA-08 authors is more toxic and costly and likely no more efficacious compared to sdTMZ.

The very recently published Nordic randomized trial (342 patients enrolled, 291 randomized) that compared sdTMZ to sdRT to hypoRT (30 Gy in 10 fractions) in elderly GBM patients (defined as age >60 years and KPS ≥ 50) suggests sdTMZ is equivalent with respect to survival when compared to the hypoRT and superior to sdRT (60 Gy in 30 fractions) treatment arm [median survival 8.3 vs. 7.5 vs. 6 months] [29]. Based upon this prospective study, it would appear treatment with

Table 4 Clinical trials in elderly glioblastoma

Trial (Reference)	Age (years)	Number	Treatment							Median overall survival (months)
			RT60	RT50	RT40	RT34	RT + TMZ	TMZ	BSC	
EORTC/NCIC [1]	60–70	173	x				x			10.9/11.8
NCIC [7]	>70	95	x		x					6.1/5.6
French [6]	>70	81		x					x	6.6/3.5
NOA-08 [18]	>65	412	x					x		9.6/8.6
Nordic [29]	60–69	100	x			x		x		7.5/7.0/7.9
	>70	191	x			x		x		5.2/7.1/9.0
ANOCEF [30]	>70 + Low PS							x		6.0
ANOCEF [31]	>70 + Low PS							x + Bev		6.0

Legend EORTC/NCIC European Organization for Research and Treatment of Cancer/National Cancer Institute, Canada, *NCIC* National Cancer Institute, Canada, *RT#* Radiotherapy total dose, *RT + TMZ* Radiotherapy plus concurrent and adjuvant temozolomide, *TMZ* Temozolomide, *BSC* Best standard of care, *Bev* Bevacizumab, *PS* Performance status

either sdTMZ or hypoRT is equivalent for elderly GBM patients and importantly evidenced-based.

In a single arm multi-institutional Phase II study of 70 patients by the French consortium ANOCEF (Association de Neuro-Oncologie d'Expression Française) in patients with GBM, age >70 years, 90 % biopsy only and KPS < 70, sdTMZ only treatment resulted in a median overall survival of 6 months conferring further evidence of chemotherapy only for newly diagnosed elderly GBM is a valid treatment [30]. Very recently, a second French ANOCEF trial in newly diagnosed elderly patients with GBM assessed the benefit of adding bevacizumab to sdTMZ and when compared to the above-mentioned ANOCEF trial found no benefit to the up-front use of bevacizumab in combination with sdTMZ compared to sdTMZ only [31]. This ANOCEF study appears to recapitulate the large RTOG 0825 and European AVAglio trials that compared SOC RT + TMZ with or with bevacizumab in young good PS patients with newly diagnosed GBM and demonstrated no overall survival advantage for the up-front use of bevacizumab [32, 33].

In a retrospective series of 233 elderly patients with GBM (median age 74 years), the German Glioma Network concluded *MGMT* promoter methylation increases with increasing age, *MGMT* promoter methylation is prognostic for mOS but not for progression free survival (PFS), *MGMT* promoter methylated tumors have improved outcome when treated with alkylator chemotherapy versus RT and *MGMT* promoter unmethylated tumors have improved outcome when treated with RT versus chemotherapy [20]. Additionally, this large series assessed *MGMT* promoter methylation by two techniques; the commercially available and most frequently used methylation specific polymerase chain reaction (MSP) and by pyrosequencing. Pyrosequencing with >25 % *MGMT* methylated alleles (50 % all MSP positive tumors) better defined the cohort of patients most likely to respond to alkylator chemotherapy versus RT. Lastly, this study suggested that combined therapy (RT + TMZ) might be superior to TMZ only in the *MGMT* methylated group of tumors, whereas there was no added benefit of combination therapy over RT only in the *MGMT* unmethylated group of tumors. This latter point recapitulates results of the EORTC/NCIC trial discussed below.

A commonly recommended and frequently utilized treatment for elderly patients with GBM is the EORTC/NCIC regimen of TMZ-based chemoradiotherapy followed by 6-months of post-RT sdTMZ, a treatment that is established as the standard of care for patients <71 years of age and with a KPS ≥ 70 [1, 34–41]. Two recent randomized Phase III RTOG trials, 0525 mentioned above and 0825, a comparison of the EORTC/NCIC regimen with or without bevacizumab in newly diagnosed high PS patients with GBM undergoing resective surgery, have not provided any survival data on specific age cohorts [19, 32]. Consequently, it is uncertain if the RT + TMZ followed by post-RT sdTMZ regimen offers any benefit in elderly GMB patients, defined as patients >70 years and perhaps as young as >65 years of age, as compared to sdTMZ only or hypoRT.

In a subset analysis of the EORTC/NCIC trial, promoter methylation of the MGMT conferred a survival benefit suggesting both prognostic and predictive value of the MGMT promoter methylation status [13]. Importantly, this was confirmed prospectively in the RTOG 0525 trial [19]. Both trials suggested approximately 30 % of all newly diagnosed GBM are MGMT methylated and it is these patients which appear to gain benefit from the inclusion of TMZ. By contrast, the role of TMZ in the nonmethylated group is uncertain and lacking alternative therapies, both methylated and unmethylated GB patients continue to be treated with RT + TMZ regimen outside of clinical trials [3, 21, 22]. The German NOA-08 study ascertained MGMT methylation in a subset of patients (35 %) and determined that ddTMZ conferred a benefit with respect to event-free survival (statistically significant) and overall survival (trend only) compared to sdRT only (median survival 8.4 vs. 4.6 months) suggesting MGMT determination may be relevant for treatment decisions in elderly patients with GBM [18]. Similarly, the Nordic trial assessed MGMT status in 75 % of all patients and demonstrated a survival benefit in patients with MGMT methylated promoter when treated with sdTMZ as compared to unmethylated MGMT (median survival 9.7 vs. 6.8 months) [29]. MGMT promoter status (methylated or unmethylated) did not affect survival in patients treated with either RT treatment arm [28]. This conclusion is similar to that of the EORTC/NCIC trial and despite which patients with newly diagnosed GBM continue to be treated outside of clinical trials with RT + TMZ followed by post-RT sdTMZ [13]. It is unlikely another trial of newly diagnosed GBM will be conducted comparing RT to RT + TMZ that is powered sufficiently to conclusively demonstrate that TMZ is beneficial only in MGMT methylated tumors. However, the German NOA-08 and Nordic trials provide further evidence that TMZ is particularly beneficial in the MGMT methylated tumor subset [41]. A practical issue is whether an unspecified endpoint that is response of tumors based upon MGMT methylation status as determined in the German NOA-08 and Nordic trials changes clinical practice or even clinical trial design. It is worth mentioning that the determination of MGMT in the seminal EORTC/NCIC trail was a retrospective analysis, the results of which profoundly influenced treatment of GBM. This is particularly relevant as the NCIC/EORTC is currently conducting a randomized trial in elderly patients with GBM defined as patients >65 years of age comparing hypoRT (40 Gy in 15 fractions) with (concurrent and adjuvant) or without sdTMZ [42]. The NCIC/EORTC elderly GBM trial included MGMT promoter methylation as a prospective stratification factor. If upon completion of the trial hypoRT only is inferior therapy in elderly patients with methylated MGMT tumors, this treatment arm would then be reserved for elderly patients with unmethylated MGMT tumors assuming there is no added benefit to combination therapy in this cohort. Response based upon MGMT methylation status was never powered sufficiently in the seminal EORTC/NCIC trial to answer the question unequivocally regarding the benefit of RT + TMZ. Nonetheless, there appears to be compelling evidence that TMZ adds benefit only to the MGMT methylated cohort of newly diagnosed GBM suggesting that treatment practice changes to include MGMT methylation determination when considering either hypoRT or sdTMZ only for elderly patients

Table 5 Treatment categories of elderly patients with glioblastoma

Category	Preferred treatment
Physiologically young (geriatric scale assessment)	Hypofractionated radiotherapy in unmethylated MGMT tumors
	Standard dose temozolomide in methylated MGMT tumors
Frail with good performance	Hypofractionated radiotherapy or standard dose temozolomide only
Compromised performance	No treatment or hypofractionated radiotherapy

outside of a clinical trial. Determining a standard of care for elderly patients with newly diagnosed GBM would constitute a significant achievement and based upon the NOA-08 and Nordic trials that realization appears closer.

3 Summary

In conclusion, elderly patients with GBM appear at this juncture based upon available prospective evidence to benefit from either hypoRT or TMZ only with deferred RT (Table 5) [43]. The benefit if any of combination therapy (RT + TMZ) in the elderly will be adjudicated in the soon-to-be-completed NCIC/EORTC trial. Because determination of the tumor promoter MGMT methylation status appears both prognostic as well as predictive in the elderly, assessment of MGMT methylation is important in determining best therapy (hypoRT vs. sdTMZ) and consequently should become a standard practice in the elderly with GBM.

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