TOPIC REVIEW

Impact of therapy on quality of life, neurocognitive function and their correlates in glioblastoma multiforme: a review

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Abstract The maintenance of quality of life (QoL) in patients with high-grade glioma is an important endpoint during treatment, particularly in those with glioblastoma multiforme (GBM) given its dismal prognosis despite limited advances in standard therapy. It has proven difficult to identify new therapies that extend survival in patients with recurrent GBM, so one of the primary aims of new therapies is to reduce morbidity, restore or preserve neurologic functions, and the capacity to perform daily activities. Apart from temozolomide, cytotoxic chemotherapeutic agents do not appear to significantly impact response or survival, but produce toxicity that is likely to negatively impact QoL. New biological agents, such as bevacizumab, can induce a clinically meaningful proportion of durable responses among patients with recurrent GBM with an acceptable safety profile. Emerging evidence suggests that bevacizumab produces an improvement or preservation of neurocognitive function in GBM patients, suggestive of QoL improvement, in most poor-prognosis patients who would otherwise be expected to show a sudden and rapid deterioration in QoL.

Introduction

High-grade gliomas, WHO grade III or IV [1, 2], are the most common primary brain tumors in adults [1, 3]. WHO grade IV tumors are almost exclusively (80–90%) glioblastoma multiforme (GBM), which are the most common high-grade glioma (40–45%) [1, 3], the most common form of brain tumor overall (12–15%) [1, 3], and the most aggressive malignant primary brain tumor [4]. Despite limited significant advances in standard therapy, notably temozolomide, median overall survival (OS) remains low: 15 months for newly-diagnosed GBM [5, 6] and 5–7 months for recurrent/relapsed GBM [7–10]. In a clinical trial setting, the current standard of care (radiotherapy plus temozolomide followed by 6 cycles of adjuvant temozolomide) provided 2- and 5-year survival rates of 27 and 10% for patients with newly diagnosed GBM [6]. Thus, an unmet medical need for improved therapeutic options remains.

Given the poor prognosis of GBM, the primary objectives of therapy are to reduce morbidity, restore or preserve neurologic functions and the capacity to perform daily activities as long as possible [11]. The aim of this review is to examine the impact of GBM therapy on QoL, neurocognitive function, and their correlates.

Neurocognitive functioning and QoL

It is well recognized that impairment of neurocognitive functioning, resulting in behavioral, emotional, and

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intellectual difficulties, occurs in nearly all patients with brain tumors and eventually compromises their independence [12]. This impairment is related to a combination of various factors, including the tumor itself, tumor-related epilepsy, treatment, and patient-related factors (e.g., age, psychological distress) [13–16]. However, there have been relatively few well-powered longitudinal studies of neurocognitive function in patients with high-grade glioma [17]. Neurocognitive function is an important determinant of QoL [18–20]. Not surprisingly, neurocognitive function assessments have been incorporated as major components of patient assessments, along with common and widely used questionnaires to assess health-related QoL (HR-QoL), e.g., European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30), and Functional Assessment of Cancer Therapy (FACT) cancer-specific scales [21]. Indeed, neurocognitive function has been shown to be a valid predictor of long-term QoL [22–24].

As life expectancy in high-grade glioma, and particularly in recurrent GBM, is so short, issues relating to QoL are immensely important to patients and their caregivers [17]. This is especially important in relation to new treatments in recurrent GBM that do not yet have evidence supporting their contribution to extended survival but may significantly delay the expected steep QoL deterioration occurring after progression following standard therapies [17]. Unfortunately, QoL data are difficult to collect in cancer patients because they may be unwilling to complete the questionnaire when they are feeling unwell. Furthermore, repeated application of lengthy, formal HR-QoL questionnaires can represent a major and impractical burden for patients [25]. Also, the analysis of QoL data is challenging due to the high rates of non-random missing QoL values that may be linked to patients' QoL status, and if ignored may introduce bias in the interpretation of results [26]. Interpretation of the impact of standard and new therapies on QoL in GBM patients is consequently problematic, even when attempting to classify their effect into the three broad categories of negative, positive, or neutral.

To overcome these challenges, changes in neurocognitive functioning may be taken as a proxy for QoL changes. Assessment of neurocognitive function can therefore represent a practical surrogate for formal QoL assessment of patients with recurrent GBM. In addition, besides grade and age, performance status in patients with newly diagnosed glioma is an independent prognostic marker. Thus, it is plausible to assume that neurocognitive function, irrespective of clinical stage, may also have prognostic implications even after initiation of therapy and during the course of treatment.

Treatment impact on QoL and its correlates

HR-QoL in patients with high-grade glioma has recently been reviewed in detail [17], which noted problems associated with interpretation of different studies and the paucity of robust HR-QoL information derived from well-powered randomized controlled trials. Among the seven randomized controlled trials of new treatments published from 2002 to 2007 they identified for high-grade glioma, there was no or little difference between treatment groups at baseline or follow-up evaluation. These authors suggested that standard multidimensional HR-QoL questionnaires might therefore contain too many items and consequently lack sensitivity to detect QoL changes in patients with high-grade glioma. Simpler, practical, and more sensitive instruments (such as cognitive function) are therefore needed to study QoL changes in relation to therapy in high-grade glioma, and, thus, the confounding factor of missing substantial follow-up data (primarily related to dropouts) needs to be addressed.

Standard therapy

Neurosurgery and/or radiotherapy are still fundamental elements of standard therapy for patients with high-grade glioma. It is well recognized that surgery may initially, at least temporarily, improve QoL dramatically in a significant proportion of patients with severe symptoms related to increased intracranial pressure [3]. Conversely, radiotherapy may decrease QoL in some patients from adverse effects such as hair loss, fatigue, somnolence, or cognitive problems [26]. The influence of radiotherapy on neurocognitive function has recently been reviewed [27]. It is clear that tumor recurrence and short-term survival are confounding variables, but it is generally agreed that short-term memory and progression of dementia are observed in many patients treated with brain irradiation. The impact of adjunctive therapy with corticosteroids and antiepileptic medication has also been extensively studied. While the presence and severity of epileptic seizures and/or the use of antiepileptic medication have been significantly associated with cognitive deficits in patients with low-grade gliomas, more so than the effects of radiotherapy [28–30], the effects of antiepileptic medication on neurocognitive functioning and QoL have been less extensively studied in patients with high-grade glioma, although some studies have reported a negative impact [31].

The negative effects of corticosteroid use on neurocognitive function and/or QoL are well documented in healthy subjects [32, 33] and in various disease states, such as leukemia [34]. While it appears accepted that the use

of high-dose corticosteroids has a clinically significant negative impact on neurocognitive function in glioma, there would appear to be no published information in this indication. However, it is documented that corticosteroid use in primary brain tumors and/or metastases caused adverse effects [35, 36] which would be expected to decrease QoL.

Assessment of QoL is important with cytotoxic chemotherapy, particularly when survival benefit may be marginal and has to be balanced against any negative contribution of significant toxicity. Among newly diagnosed GBM patients randomized to radiotherapy alone or radiotherapy plus temozolomide, the addition of temozolomide had no significant negative effect on QoL measures, except on social functioning ($p = 0.0052$) [37]. Similarly, among first-relapse GBM patients, temozolomide had no significant negative effect on QoL, although responders to temozolomide had improvement in most QoL domain scores, e.g., global, motor dysfunction, emotional function, drowsiness, future uncertainty, and communication deficit, until eventual disease progression [38–40]. These overall findings with temozolomide in GBM are concordant with the recent Cochrane review that evaluated randomized controlled trial data assessing temozolomide in patients with high-grade glioma [41].

When used as a comparator for temozolomide among the aforementioned trials, procarbazine was reported to have a negative impact on HR-QoL domain scores, e.g., drowsiness, communications deficit, motor dysfunction, role functioning, social functioning, and physical functioning, regardless of disease progression status [38, 39]. The impact of combined procarbazine, CCNU (lomustine), and vincristine (PCV) chemotherapy after radiotherapy compared with radiotherapy alone on HR-QoL measures was determined in the EORTC 26951 trial of patients with anaplastic oligodendroglioma ($n = 368$): a major negative impact on HR-QoL (nausea/vomiting, appetite loss, and drowsiness) was found during and shortly after PCV treatment [42]. However, when HR-QoL measures were used to assess the impact of PCV chemotherapy after radiotherapy compared with radiotherapy alone in the Radiation Therapy Oncology Group (RTOG) trial 94-02 of patients with mixed anaplastic oligodendroglioma, scores were similar longitudinally and between treatments for survivors [43]. HR-QoL (Spitzer Quality of Life Index) score showed continual deterioration when measured longitudinally in the RTOB 98-03 study of escalating doses of conformal three-dimensional radiation and carmustine in GBM patients [44]. Supplementation of surgery and radiotherapy with CCNU chemotherapy provided no benefit in terms of quality of life or change in clinical performance [45]. Finally, there are very limited QoL data from randomized controlled trials with implanted

carmustine-impregnated wafers in primary or recurrent high-grade glioma according to a recent Cochrane review [46].

New and investigational GBM therapies

Bevacizumab (Avastin®), a humanized monoclonal antibody that binds to and inhibits the activity of VEGF, is the first approved antiangiogenic cancer treatment. Bevacizumab acts synergistically with cytotoxic chemotherapy or biological agents in the treatment of various tumors, e.g., colorectal, lung, renal, and breast cancer [47–50]. Recently, studies in patients with recurrent high-grade glioma or GBM have indicated promising results with durable response using the combination of bevacizumab and irinotecan [51–67], and additionally in combination with etoposide [68], nitrosourea [69], fotemustine [70], or erlotinib [71]. Positive results have also been reported with single-agent bevacizumab in recurrent high-grade glioma [57, 61, 72–74], and in combination with adjuvant temozolomide in newly diagnosed GBM [75–79].

During these studies of bevacizumab-based therapy in high-grade glioma, it was reported that one of the consequences of bevacizumab therapy is a steroid-sparing effect in a proportion of patients, which would be expected to positively impact QoL. Various studies have indicated a reduction or elimination of corticosteroid use with bevacizumab-based therapy in patients with recurrent high-grade glioma after prior treatment [53, 56–61, 63, 64, 73]. For example, in the randomized phase II clinical trial comparing bevacizumab alone or in combination with irinotecan in 167 patients with recurrent, treatment-refractory GBM [61], patients who were taking corticosteroids at baseline showed a trend to take stable or decreasing doses over time, e.g., median corticosteroid dose was reduced by about 75% after 6 months (Fig. 1). The steroid-sparing effect associated with bevacizumab-based therapy appeared associated with clinical response in high-grade glioma [58, 64] and clinical benefit such as improved neurological symptoms in high-grade glioma [59] or recurrent GBM [73].

A potentially positive impact of bevacizumab-based therapy on neurocognitive function, performance status and/or QoL has also started to emerge from reports of clinical studies among GBM patients [52, 59, 63, 64]. For example, in a retrospective analysis of recurrent GBM patients treated with bevacizumab ($n = 44$) or without bevacizumab ($n = 79$) at a single US institution [63], it was reported that bevacizumab-treated patients took longer to increase dexamethasone dose (median 149 vs. 130 days, $p = 0.04$) and also maintained their Karnofsky Performance Status (KPS) for longer (median 252 vs. 120 days, $p = 0.006$); subgroup analysis indicated that the difference
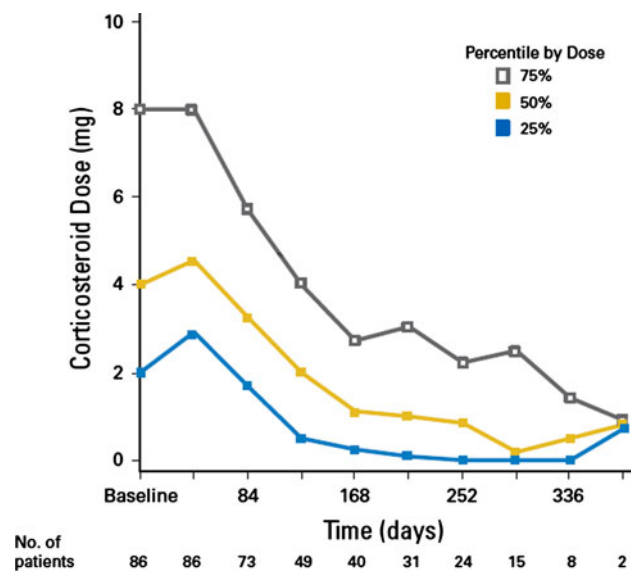
Fig. 1 Change in median corticosteroid use following treatment with bevacizumab with or without irinotecan in patients with recurrent glioblastoma multiforme (adapted with permission from Friedman et al. [61])

in these effects were more pronounced in patients aged >55 years. In another study of 22 consecutive patients with recurrent GBM treated with bevacizumab plus irinotecan [52], cognitive function was assessed by the Blessed Orientation-Memory-Concentration Test (BOMC) and functional status was assessed by KPS, Barthel Index (BI), and Instrumental Activities of Daily Living (IADL) prior to each cycle of treatment. Improvement in BOMC score was seen in 15 patients (62%), with median improvement of 7 points. Improvement in functional status was seen in 18 patients (85.7%), with median improvement in KPS by 10 points, BI by 8 points, and IADL by 2 points. The overall clinical response rate with bevacizumab plus irinotecan was 95% and was associated with significant improvements in cognitive functional and functional status.

Larger scale controlled clinical trials of bevacizumab-based therapy in GBM patients were consequently undertaken or are planned/on-going. Among these is the recently reported BRAIN study (AVF3708g), an open-label, multicenter, randomized, phase II trial of two concurrent arms treated with single-agent bevacizumab (n = 85) or bevacizumab plus irinotecan (n = 82) in patients with first- or second-relapse GBM who had been previously treated with temozolomide initially or at relapse. Primary endpoint results have been reported: estimated 6-month PFS rates were 43 and 50% in single-agent bevacizumab and bevacizumab plus irinotecan arms, respectively, and objective response rates were 28 and 38%, respectively [61]. These results supported the activity of bevacizumab in recurrent GBM patients given that the 6-month PFS rate was

considerably higher than the 15% rate expected for salvage chemotherapy and/or chemotherapy alone. The authors noted a trend for patients who were taking corticosteroids at baseline to take stable or decreasing doses over time, but they made no formal comparison.

More compellingly data on corticosteroid use during this study have recently been reported [80]. At baseline, 51 and 53% of patients received systemic corticosteroids in the single-agent bevacizumab and bevacizumab plus irinotecan arms, respectively. More than 75 and 65% of patients in the single-agent and combination arms, respectively, who did not receive corticosteroids at baseline continued to receive no corticosteroids after baseline. Sustained reduction in corticosteroid use was defined in this study as a ≥50% dose reduction for ≥50% of time on study treatment up to 52 weeks. Among patients with complete or partial response in the single-agent bevacizumab and bevacizumab plus irinotecan arms, 57 and 65%, respectively, had a sustained reduction in corticosteroid use compared with 17 and 38%, respectively, among those with stable or progressive disease.

Neurocognitive function of patients treated with single-agent bevacizumab in the BRAIN study (n = 85) has been analyzed [81]. Patients were assessed with the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test parts A (TMTA) and B (TMTB), and the Controlled Oral Word Association (COWA) test. Assessments were conducted at baseline and then every 6 weeks while patients remained on study treatment up to 52 weeks. Change in neurocognitive function from baseline to week 6 was categorized as improved, stable, or declined, using the reliable change index. Between 93 and 98% of patients completed each test at baseline and 73–78% completed each test at both baseline and week 6. The majority of patients demonstrated stable performance on each test at week 6, relative to baseline. With the exception of the COWA test, 16–28% of patients demonstrated improved performance on one or more tests at week 6 (Table 1). Preliminary results suggest that the majority of patients with recurrent GBM who were treated with bevacizumab alone in the BRAIN study demonstrated stable or improved neurocognitive function during the first 6 weeks of treatment (81–100% across all tests). Changes across tasks and associations with measures of clinical efficacy were also explored (Table 2).

In a recent retrospective analysis [82], 12 patients with GBM and poor neurologic function (KPS <60%) due to bulky disease were treated in an up-front setting with bevacizumab following induction temozolomide in an attempt to improve their ability to tolerate chemoradiation. Median KPS improved from 50 to 70% and their median dexamethasone dose was reduced from 12 to 4 mg/day. Five of 11 evaluable patients (45%) had a partial response,

Table 1 Neurocognitive changes in patients with recurrent glioblastoma receiving single-agent bevacizumab in the BRAIN study

Assessment	Change in performance at week 6 relative to baseline (per Reliable Change Index)		
	Improved (%)	Declined (%)	Stable (%)
HVLT-R total recall ($n = 74$)	16	18	66
HVLT-R delayed recall ($n = 70$)	14	16	70
HVLT-R delayed recognition ($n = 69$)	22	19	59
TMTA ($n = 73$)	23	11	66
TMTB ($n = 65$)	28	11	62
COWA ($n = 70$)	3	0	97

HVLT-R Hopkins Verbal Learning Test-Revised, *TMTA* Trail Making Tests part A, *TMTB* Trail Making Test part B, *COWA* Controlled Oral Word Association test

Table 2 Stabilization or improvement in neurocognitive function in patients with recurrent glioblastoma receiving single-agent bevacizumab in the BRAIN study

	Stable/improved neurocognitive function on all tests n (%)	Deterioration in neurocognitive function in at least one test n (%)
Responders at time of IRF response ($n = 24$)	18 (75%)	6 (25%)
PFS >6 months at week 24 ($n = 27$)[a]	19 (70%)	8 (30%)
Patients at time of investigator PD ($n = 49$)[b]	15 (31%)	34 (69%)

IRF independent radiology facility, *PFS* progression-free survival, *PD* progressive disease

[a] Two patients had missing neurocognitive data and were dropped from the analysis

[b] Eight patients had missing neurocognitive data and were dropped from the analysis

4 (35%) a minor response, and 1 (10%) stable disease. Median TTP and OS were 5.2 and 8 months, respectively. The tumor response, rapidly improved neurologic function, and reduced steroid requirement allowed the majority of patients (75%) to complete definitive radiotherapy.

Little significant information appears to have been published on the effects of other investigational biological agents (e.g., cilengitide, cediranib, sorafenib, sunitinib) on corticosteroid use, neurocognitive function, or QoL in patients with high-grade glioma or more specifically those

with GBM. In a recent phase II study of cediranib [83], an oral pan-VEGFR tyrosine kinase inhibitor, was administered as monotherapy (45 mg/day) in 31 patients with recurrent GBM and resulted in encouraging proportions of radiographic partial responses of 57 and 27% on 3- and 2-dimensional MRI, respectively) and 6-month PFS (26%). Furthermore, among 15 patients receiving corticosteroids on study entry, the dose was reduced ($n = 10$) or discontinued ($n = 5$).

Conclusions

Maintenance of QoL in patients with high-grade glioma is an important endpoint during treatment, and more so for GBM because of the particularly poor prognosis with short life expectancy at this stage of the disease. However, reliable serial measurement of QoL in patients with high-grade glioma is notoriously difficult, relating to many factors but particularly dropout bias or inability to repeatedly complete complex forms. It would appear that there is a progressive decrease in QoL during the course of high-grade glioma that substantially accelerates once the disease relapses. This is also expressed as deterioration peaks driven by the administered therapies (e.g., radiotherapy) or by the exacerbation of accompanying syndromes (e.g., brain edema, neurological symptoms, psychiatric disturbances).

It has proven difficult to identify new therapies that extend OS and PFS in patients with recurrent GBM after failure of previous therapy. Most alternative cytotoxic chemotherapeutic agents do not seem to significantly impact response or survival, yet may produce adverse effects that have a likely negative impact on QoL. However, among the new biological agents, bevacizumab has been shown to induce a clinically meaningful proportion of durable responses among patients with an acceptable safety profile. Furthermore, data are emerging that bevacizumab induces improvement or preservation of neurocognitive function, suggestive of QoL improvement, in the majority of poor-prognosis patients who would otherwise be expected to show a sudden, rapid deterioration in QoL. Further studies are underway to confirm these findings and better understand the natural history of the QoL of these patients.

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