High Costs, Low Quality of Life, Reduced Survival, and Room for Improving Treatment: An Analysis of Burden and Unmet Needs in Glioma

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Background and Methods

- Gliomas are the most frequent malignant brain tumor, of which glioblastoma is the most severe histological type, diagnosed in up to 60–80% of patients [1,2]
- Survival in patients with glioma is often poor: 5-year net survival has been estimated at 4–17% for glioblastoma and is only 32–69% even in oligodendroglioma despite improvements in survival in the last 10–25 years [3,4]
- Beyond poor survival, significant unmet needs exist in patients with glioma, notably for treatment as 1L treatments are often associated with toxicity while 2L treatment is unstandardized
- The present study reviewed the literature on unmet needs and the burden of glioma more broadly, with the aim of providing an overview of the field primarily for a non-clinical audience, e.g., researchers involved in health technology assessment
- Treatment guidelines for glioma were also reviewed, with a focus on the role of lomustine, the SOC for recurrent glioblastoma [5]

Results: Humanistic and Economic Burden of Glioma

- After a glioma diagnosis, quality of life of patients and their caregivers is significantly reduced.
- Healthcare payers and societies face substantial direct and indirect glioma-, particularly glioblastoma-associated costs.

Item	Summary of findings from the literature
Humanistic burden	
QoL with glioma	• Generally, QoL is reduced with glioma, mainly due to disease symptoms, which include neurocognitive deficits (such as visual disorders and problems communicating), disturbed sleep, fatigue, drowsiness, reduced bladder control, and itchy skin [15–20] • For up to 81% of patients, QoL is the most important factor in treatment decisions, and 79% value QoL over survival at diagnosis [21]
Change in QoL	• QoL tends to remain stable after surgery or improves slightly in the long term, including in low-grade glioma [15, 22] and glioblastoma [23] • Advanced/high-grade gliomas more likely lead to worse QoL and mood disorders than low-grade gliomas, they are also more likely to be associated with deteriorating QoL while QoL in lower-grade gliomas often remains stable [24–26]
Treatment QoL	• There were no significant QoL differences when comparing lomustine with regorafenib [27] or as an add-on to TMZ [28] • There was no significant QoL difference between patients with low-grade glioma receiving RT or TMZ [29]
Support for patients and caregivers	• Patients consider the feeling of being listened to and receiving psychological support to be important, but they (and their caregivers) may not feel fully involved in decision-making and healthcare personnel may not routinely assess patients' mood, thereby preventing referral to psychological support [30] • Psychological support may also be lacking in palliative/end-of-life treatment, even if medical treatment is perceived to be good [31]
Economic burden	
US	• Most literature available is on the US– mean estimates of cumulative per-patient costs range from $95,377 (Medicare; driven mainly by hospitalization) for glioblastoma [12] to $184,160–268,031 (commercial, driven by in- and outpatient costs) across high-grade gliomas [32,33]. • Patients with brain cancer (not just glioma) face financial hardship, with >10% of patients or caregivers reporting delayed or unaffordable care [34]
Globally	• A 2021 review identified wide variation between countries and institutions (as well as poor reporting) of glioblastoma-associated management costs [35]: mean direct costs per patient for surgical resection, in 2017$, were $10,042 (ranging from $4,128 to $14,857), with combined surgery, chemotherapy, and RT estimated at $62,602
Productivity losses, indirect costs	• Productivity losses – due to the disease, associated depression, and the inability to return to work – account for a substantial cost burden in glioma • In the Netherlands, glioma-associated productivity losses per 4 weeks were €1,265 (patients) and €337 (caregivers), due to health problems, absenteeism, and presenteeism in 2015 [36], In Spain, overall indirect costs per patient with glioblastoma were €111,926 in 2015 [37]. • Economic losses due to premature death from brain cancer in Europe (2018) were €428,449 per premature death, due to lost paid production [38]

Results: Treatment Patterns

Many patients with glioma still receive no or inadequate care, including in:

- **China** (n=1,010; glioblastoma [8]): 54% of patients with subtotal resection (no improvement over time), while only 51% received RT with adjuvant TMZ (use of which increased over time)
- **Germany** (n=40,138; glioblastoma [9]):
  - Chemotherapy use increased over time but was still only 60% in 2011–2014 – survival increased in parallel but was still lower than expected from improved surgical techniques and use of adjuvant radio-chemotherapy
  - 5% of cases received no cancer-related treatment and 10% had only surgery
- **France** (n=1,856; glioblastoma [10]):
  - 41% received only RT after surgery, while another 20% received no further treatment
  - Of those with adjuvant treatment, only 49% completed ≥6 cycles (more cycles were associated with better OS)
- **South Korea** (n=555; WHO grade II gliomas [11]): Only 36% of patients with gross technical resection; of those without gross technical resection, 30–40% received no follow-up treatment
- **US** (n=4,308; glioblastoma [12]):
  - One in five cases received no cancer-related care; two in three cases with 1L treatment received no 2L therapy
  - Treatment access limited and treatment delayed for patients who were not White non-Hispanic [13]
- **US** (n=5,890; anaplastic astrocytoma [14]): 15% of patients received no adjuvant care

Results: Lomustine Efficacy and Safety

Efficacy

- PCV+RT improved progression-free survival and OS in an RCT versus RT alone in grade 2 glioma [51], including in high-risk, IDH-mutant disease [52]
- In another RCT, 1L PCV+RT was associated with prolonged OS versus RT alone in 1p/19q-codeleted anaplastic oligodendroglioma, pure and mixed oligoastrocytoma [53]
- Data from two RCTs suggested good disease control and survival over ~30 years of follow-up [54]
- In retrospective studies, survival was longer with PCV than TMZ in anaplastic astrocytoma, oligodendroglioma, and grade 2 gliomas [55–58]. One retrospective study reported prolonged survival with TMZ versus PCV in glioblastoma [59]
- For recurrent glioblastoma, lomustine performs as well as (OS) or better (toxicity) than most other therapies [5,60]

Safety

- Retrospective and randomized studies and reviews consistently indicate significant toxicity of PCV [55–57,61–69]
- The most important toxicity associated with lomustine is thrombocytopenia, which can prevent the use of lomustine as a salvage treatment in recurrent glioblastoma [70]
- Toxicities are dose dependent, so patients frequently have their PCV or lomustine doses reduced, delayed, or discontinued [5,66,71]
- Between 49 and 65% of patients have lomustine and vincristine doses reduced or discontinued by the sixth treatment cycle [72]

Results: Treatment Recommendations

Oligodendroglioma, IDH-mutant and 1p/19q-codeleted

WHO grade 2

- 1L: RT+PCV (TMZ if toxicity concerns) [39, 40, 42, 47]
- 2L: BSC, chemotherapy, RT±chemotherapy (depending on prior RT), TMZ [40, 47]
- **Lomustine:** Part of 1L regimen (PCV)

WHO grade 3

- 1L: RT+PCV/TMZ, else RT or TMZ [39–41,45, 48]
- 2L: BSC, chemotherapy, lomustine (including as rechallenge [43,49]), RT, surgery, systemic therapy, TMZ [40, 41, 43, 47]
- **Lomustine:** Part of 1L (PCV) and as 2L treatment (also rechallenge)

Glioblastoma, IDH-wildtype

- **1L:** RT (possibly hypofractionated)+TMZ±TTF [39–42,44,48], possibly only RT if MGMT unmethylated or poor status/elderly MGMT methylated; RT+lomustine+TMZ±TTF (in fit, younger patients with MGMT methylated) [50,73]
- **2L:** Bevacizumab, nitrosourea/lomustine, (repeat) RT systemic therapy, TMZ rechallenge, TTF [40,41,47,50]
- **Lomustine:** Potentially part of 1L treatment in fit, younger patients (MGMT methylated) and SOC 2L treatment.

Astrocytoma, IDH-mutant

WHO grade 2

- 1L: RT+PCV/TMZ [39–43, 49]
- 2L: Bevacizumab, lomustine, nitrosourea, TMZ [40–43]
- **Lomustine:** Part of 1L (PCV) and as 2L treatment

WHO grade 3

- 1L: RT+TMZ [39–43,45,48,49]
- 2L: Bevacizumab, PCV or lomustine [43], nitrosourea [40], RT, systemic therapy, TMZ rechallenge
- **Lomustine:** Part of PCV or on its own as 2L treatment

WHO grade 4

- 1L: RT+TMZ [40]
- 2L: Bevacizumab, nitrosourea, TMZ rechallenge [40]
- **Lomustine:** 2L treatment (nitrosourea)

Conclusions

- Patients with glioma and their caregivers face a substantial humanistic burden. Their QoL should be improved through better access to comprehensive supportive care
- Effective 2L treatments (notably for recurrent glioblastoma) are lacking; toxicity of existing treatments could be better managed
- The evidence base, including for treatments such as lomustine, could be improved, preferably by running additional RCTs

Abbreviations

1/2L, 1st/2nd line; BSC, Best Supportive Care; IDH, Isocitrate Dehydrogenase; OS, Overall Survival; PCV, Procarbazine, Lomustine; Vincristine. QoL, Quality of Life; RCT, Randmized Controlled Trial; RT, Radiotherapy; SOC, Standard of Care; TMZ, Temozolomide; TTF, Tumor Treating Fields; US, United States; WHO, World Health Organization.

References

The full reference list for this poster can be found online at: https://medac.covalence-research.com/Lomustine-Burden-Review/ISPOR-2023/Poster-References.docx

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