Anaplastic gliomas: end-of-life care recommendations

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Practice points

- Symptoms in the end-of-life (EOL) phase in brain tumor patients are different from patients with systemic cancers.
- EOL care in brain tumor patients comprises several aspects, such as the management of symptoms, EOL decision-making, the organization of care and caregiver burden.
- Cultural, legal and religious issues underlie differences in EOL organization, care and decision-making.
- Specifically in brain tumor patients, with a high chance of a progressive cognitive decline, it is important to timely initiate discussions regarding care and treatment in the EOL phase. For this goal, advanced care planning seems warranted and should result in improved outcomes for brain tumor patients and their caregivers.
- Care of brain tumor patients in the EOL phase should be further optimized to meet the needs of the patients and their caregivers.

Despite multimodal antitumor treatment, all patients with an anaplastic glioma will be confronted with incurability in due course and enter the end-of-life (EOL) phase; the period when the patients' condition declines and tumor-directed treatment is no longer effective. Although palliative care is important in all stages of the disease, it is of utmost importance in the EOL phase. The main goal of palliative care is to improve or maintain the quality of life of the patients and their relatives through the prevention and relief of suffering. This review focuses on different aspects of the EOL phase (symptoms and signs, EOL decision-making, advance care planning, organization of care and caregiver burden) and will provide recommendations to optimize palliative care.

Introduction

Glioma patients have an incurable disease with a poor prognosis, depending on tumor grade, histological subtype, age and performance status [1]. Although the course of disease in low-grade and anaplastic gliomas is more protracted than in glioblastoma, all infiltratively growing gliomas will undergo malignant transformation to high-grade gliomas (HGG). Despite multimodal treatment including surgery, radiotherapy and chemotherapy, every glioma patient will be confronted with incurability in due course.

Notwithstanding there is no available definition of the end-of-life (EOL) phase, it is often referred to as the period when the patient starts to deteriorate (symptom recurrence) and tumor-directed treatment is no longer possible [2–4]. It is generally confined to the last 3 months of life [5]. Although palliative care is important in all stages of the disease, it is of utmost importance in the EOL phase (Figure 1). The main goal of palliative care is to improve or maintain the quality of life (QoL)

KEYWORDS

- advance care planning
- brain tumor • caregiver burden • end of life • end-of-life decision-making
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Figure 1. Models of palliative care. The traditional model on top shows an acute transition from life-prolonging (curative) treatment into hospice care, once tumor treatment is no longer effective. In the revised model on bottom, palliative care is already installed from diagnosis, going along with life-prolonging (curative) treatment, and becomes increasingly important over time. This 'trajectory' model also includes family bereavement.

Adapted from [7].

of the patients facing a life-threatening illness and their relatives [6] through the prevention and relief of suffering. In deciding which (palliative) treatments to opt for, the benefits of the treatment have to be carefully weighed against the disadvantages.

This review will focus on different aspects of the EOL phase (Figure 2) in glioma patients and will provide recommendations to optimize palliative care.

Symptoms & signs in the EOL phase

The disease course of patients with brain tumors is different from that of other malignancies, because brain tumor patients not only have cancer but also a progressive neurological disease. This is also reflected in the symptoms these patients experience in the EOL phase. Patients with primary brain tumors report significantly less often symptoms such as pain, nausea, vomiting, dyspnea, constipation and loss of appetite when compared with a general palliative care population [8]. Considering other general cancer symptoms, however, no significant difference between glioma patients and patients without malignant brain disease was found for fatigue

(67 vs 65%, respectively) and weakness (80 vs 83%, respectively) [8]. Relief and prevention of these general symptoms are described in several guidelines. These guidelines include, among others, the prescription of analgesics such as paracetamol and opioids for pain [9,10], antiemetics for nausea and vomiting [9,11], opioids for dyspnea [9,12] and laxatives for constipation [9,11]. Loss of appetite may have several underlying causes which are treatable with medication, but otherwise it is important to realize that forced feeding and hydration, by tube or intravenous drip, is of limited use and that loss of appetite is part of the EOL process [11]. However, in one series, the majority (87%) of the brain tumor patients in the EOL phase did receive artificial hydration and tube feeding was administered in 13% of the patients [13].

Several disease-specific symptoms are frequent in the EOL phase of glioma patients [3,5,13]. These symptoms can be divided into four categories and will be discussed in the following sections: first, elevated intracranial pressure; second, seizures; third, cognitive deficits, confusion and personality changes and fourth, motor dysfunction, immobility and incontinence.

• Elevated intracranial pressure

The increase in intracranial pressure can be caused by tumor (recurrence) itself, tumor surrounding vasogenic brain edema and less frequently by concomitant hydrocephalus. Elevated intracranial pressure may result in headache, nausea and vomiting, visual disturbances, drowsiness and decreased consciousness. Headache is an often reported symptom in the EOL phase of glioma patients, ranging from 23 to 62% [3,5,13–15]. Nausea and vomiting was less frequently reported, with prevalences ranging from 6 to 33% [3,5,14,15], as were visual deficits (21%) [15]. Drowsiness or loss of consciousness, on the other hand, was present in 81–94% of the brain tumor patients in the EOL phase [2,3,13,14].

Headaches and nausea due to elevated intracranial pressure can be relieved by administration of analgesics and antiemetics. Of more importance, corticosteroids (generally dexamethasone) are prescribed to relieve the symptoms of elevated intracranial pressure by reduction of vasogenic edema. In the EOL phase, the far majority of the patients with HGG receive corticosteroids [3,5,14] that are effective in reducing symptoms of elevated intracranial pressure in the majority of the patients. However, due to progressively decreased

consciousness in the EOL phase, oral administration of corticosteroids is often discontinued in these patients. Although acute withdrawal of corticosteroids may result in a recurrence of symptoms due to an increase of intracranial pressure or may lead to acute adrenal insufficiency [16], it may also be beneficial in limiting a far from meaningful final phase of the disease.

Other methods to reduce intracranial pressure that may ultimately be considered if the effect of corticosteroids are insufficient, are ventricular shunting and osmotherapy leading to osmotic diuresis [16], but this is hardly ever warranted.

• Seizures

Epileptic seizures are common in the EOL phase of brain tumor patients, with prevalences up to 56% [2–3,5,13–15,17]. In the last month before death, most seizures are focal (79%), with a smaller proportion of patients having generalized seizures (18%) or status epilepticus (3%) [17]. Patients with a previous history of seizures have a significantly higher risk of seizures in the last month before death compared with patients who were seizure free during the disease course [17]. However, seizures may also occur *de novo* in the last month of life in HGG patients [17].

Figure 2. Overview of aspects in the end-of-life phase.

EOL: End of life.

If seizures occur in brain tumor patients, treatment with daily antiepileptic drugs (AEDs) will be initiated. There is no evidence favoring the prescription of prophylactic AED in brain tumor patients who have never had seizures. Due to possible side effects of AEDs, and the interaction with other medication, prophylactic prescription of AEDs in these patients should be discouraged [18]. On the other hand, the high prevalence of seizures in the EOL phase of brain tumor patients suggests that AEDs should be continued until death in patients who experienced seizures previously. Since oral intake of AEDs in the EOL phase may be hampered by dysphagia and/or decreased consciousness, as demonstrated in a study in HGG patients of whom only 18% was able to swallow anticonvulsants in the last days before death [17], alternative routes for AED administration should be considered [19]. One alternative route for daily use is rectal administration, for which carbamazepine, valproic acid and phenobarbital are available. More elegantly, AEDs may also be administered by intranasal spray (midazolam) or in sublingual or buccal liquid form (clonazepam). Also, subcutaneous infusion with midazolam is a possibility if a patient is admitted to the hospital, intravenous administration of AEDs is readily available [19].

• Cognitive deficits, confusion & personality changes

Prominent features in patients with brain tumors are cognitive deficits. Cognitive deficits can be caused by tumor (re)growth, tumor-related epilepsy and treatment (including surgery, radiotherapy, chemotherapy and the use of AEDs and corticosteroids) or psychological distress. In many patients, a combination of these factors will result in cognitive dysfunction [20]. In glioma patients, the cognitive deficits generally are global in character and not restricted to the brain area where the tumor is located. This may be explained by the diffuse infiltrative growth of tumor cells into the normal brain tissue [20]. Glioma patients may therefore experience a wide range of cognitive deficits.

During the disease course, more than half of the patients (54%) experience cognitive impairment according to neuropsychological assessments [21]. In the EOL phase, cognitive deficits were reported in 33% of a Dutch population of HGG patients and included memory loss, personality changes, apathy, dysphatic problems and decreased executive functioning [3].

Concentration problems were reported in more than half of the HGG patients in a study conducted in Austria [2]. Apart from cognitive deficit, the occurrence of agitation, confusion or delirium ranged from 15 to 51% in the EOL phase of brain tumor patients [3,8,13–15]. Impaired communication, probably due to both decreased consciousness, confusion and dysphasia, was reported in 64 [15] to 90% [14] of the patients.

Cognitive deficits, confusion and personality changes caused by the brain tumor and its treatment may be hard to treat. Although treatment of brain edema with corticosteroids (generally dexamethasone) may result in improvement of functioning, these drugs might also cause agitation and confusion [20]. Agitation and confusion in the EOL phase may be controlled by the use of psychopharmacological (neuroleptic) or sedative drugs [5,13].

• Motor dysfunction, immobility & incontinence

In addition to cognitive deficits, the brain tumor itself as well as its treatment can cause motor dysfunction and immobility. Hemiparesis due to the tumor, proximal leg weakness due to corticosteroids, and also loss of coordination or sensory problems may result in immobility, with a negative impact on the QoL of the patient [22]. Moreover, immobility may result in the inability of personal care and may lead to bodily pain. Incontinence is an additional burden.

In the EOL phase of brain tumor patients, poor mobility (including poor balance, falls, dizziness, difficulty mobilizing and ataxia) was reported in 77% of the patients [15]. Hemiparesis and poor coordination were reported in 62–80% [8,15] and 39% [15] of the brain tumor patients, respectively. Progressive neurological deficits, described as motor deficits, coordination loss and dysphasia, were reported in 51% of HGG patients in the last 3 months before death [3]. Furthermore, incontinence was reported in 28–40% of the brain tumor patients and bodily pain in 25% [2,3,15].

Thus, motor dysfunction is common in the EOL phase. Both cognitive and motor dysfunction will result in increased problems in activities of daily living, which were found in 93% of the primary brain tumor patients in palliative care settings [8].

Not all symptoms caused by motor dysfunction can be treated. In case motor dysfunction is caused by edema surrounding the brain tumor,

dexamethasone might effectively relieve symptoms, but this medication may unintentionally lead to proximal leg weakness. Moreover, adequate positioning of the patient and physiotherapy may be important for relief of pain caused by immobility or spasticity.

EOL decision-making

When tumor-directed treatment is no longer possible, the main goal of treatment shifts from primary life prolonging to primary supportive. The main goal in the EOL phase is to maintain the QoL of patients through prevention and relief of suffering. In this phase, patients and their relatives will be confronted with medical end-of-life decisions (ELDs). These ELDs include: first, the withholding or withdrawing of life-prolonging treatment (such as fluid and nutrition, and dexamethasone); second, alleviation of pain and other symptoms with the administration of drugs with a potential or certain life-shortening effect; third, palliative sedation and fourth, physician assisted death or euthanasia [4,23].

The frequency of deaths preceded by an ELD differed between European countries, ranging from 23% in Italy to 51% in Switzerland, and was influenced by cultural and religious standards [24]. Moreover, ELD making was found to be related to the care setting where patients die [25]. For example, nontreatment decisions were more frequently taken in the hospital setting compared with palliative care settings or at home.

A study on decision-making in HGG patients showed that at least one ELD was made in 72% of the patients [4]. Moreover, a study on palliative care needs in primary brain tumor patients showed that a hospice discussion was initiated in 85% of the patients [26]. However, the translation into so-called advance directives (i.e., legal documents in which the patient's future healthcare decisions are written) ranged largely from none to 42% of patients [2,4,13,14]. Nevertheless, 65% of the primary brain tumor patients did have a do-not-resuscitate order [26].

Compared with other cancer patients, physicians discussed EOL preferences less often with HGG patients and possibly postponed these ELDs until the last week before death [4,27]. This may especially be problematic in brain tumor patients who often have a decreased decision-making capacity due to cognitive disturbances, somnolence, delirium, dysphasia or loss of consciousness. The proportion of HGG patients

who are competent to participate in ELD making decreases considerably toward death. In a population of HGG patients, 20% was found to be incompetent in the last 3 months before death, whereas more than half (52%) of the patients was incompetent in the last week and 85% in the last days before death [4].

• Nontreatment decisions

Nontreatment decisions include withholding or withdrawing of life-prolonging treatment that is no longer considered to be meaningful or effective in the given circumstances. In the general cancer population, nontreatment decisions often concern withholding or withdrawing cardiopulmonary resuscitation, antibiotic treatment for an infection, administration of artificial fluids and nutrition, and withholding admission to the intensive care unit or a hospital. Withholding antibiotic treatment as well as nonadmission to the hospital was decided on in approximately 10% of HGG patients. Decisions on withholding artificial administration of fluid and nutrition were made in 9% [4].

Another important issue for brain tumor patients in the EOL phase is withholding or withdrawing of dexamethasone or AEDs. In both a Dutch and Italian cohort of brain tumor patients, dexamethasone was withdrawn in about half of the patients (51 and 45%, respectively) [4,13]. Although only a minority (18%) of the HGG patients were able to swallow AEDs in the last days before death [17], data on the frequency of withdrawing anticonvulsants are lacking so far. Acute withdrawal of dexamethasone or AEDs should preferably be performed if the patient has lost consciousness.

• Palliative sedation

Palliative sedation is the administration of sedative drugs in terminally ill patients who are confronted with refractory symptoms [28], without the intention to shorten life. Notwithstanding that it is often assumed that these drugs are associated with precipitation of death, no evidence is available to support this assumption [29]. Several guidelines on palliative sedation have been published and while they differ in some aspects, all include similar key recommendations. It is recommended that continuous sedation until death should only be implemented in patients with severe refractory symptoms who have a prognosis of less than 2 weeks. The medication of first choice should be a benzodiazepine, reducing

consciousness to a level that is necessary to render symptoms tolerable [30].

Palliative sedation was applied in 13% of an Italian and in 30% of a Dutch HGG population [4,13]. The explanation for differences in these percentages probably lies in complex legal, cultural and organizational factors [31].

• Physician-assisted suicide or euthanasia

The main goal of physician-assisted suicide (PAS) or euthanasia is to administer medication with the explicit intention of hastening death [23]. PAS or euthanasia is legalized in a limited number of countries (the Netherlands, Belgium, Luxembourg and Switzerland), and only allowed under strict conditions and upon a well-considered request. In a Dutch cohort of HGG patients, euthanasia or PAS occurred in 7% of the patients [4]. Although a higher percentage of HGG patients explicitly had expressed a wish for euthanasia, this request could often not be granted due to incompetence of the patient in the EOL phase.

Advance care planning

Patient autonomy is becoming increasingly important and patients often wish to be involved in treatment decisions. However, a major problem in brain tumor patients is that cognitive disturbances and communication deficits have proven to decrease the medical decision-making capacity [32] and that the majority of the patients become incompetent in the EOL phase [4]. It seems therefore important to involve patients timely in ELD making. One method to achieve this is with advance care planning (ACP). ACP is a process in which patients, in consultation with their families and physicians, make decisions regarding future goals of the EOL care. These discussions may result in the completion of an advance directive. Previously, it was found that 42% of the HGG patients in a Dutch cohort expressed their EOL preferences in an advance directive, but their physicians were not always aware of these preferences [4]. This underscores the importance to distribute advance directives among all professionals involved in the (EOL) care of the patient.

Ultimately, the goal of ACP is a higher proportion of patients in whom the EOL wishes are known and respected, also leading to a higher satisfaction with care in both patients and their families. It should be noted though that ACP is culturally sensitive and that the process and content of ACP could be different for countries

that differ with respect to legal, cultural and religious issues.

Organization of care

Patients with primary brain tumors may have a rapid illness trajectory, and experience a high symptom burden, which increases toward death. Their palliative care needs are therefore high, especially at the EOL. Palliative care services available include outpatient services such as community-based nursing, social services, complementary therapies such as speech therapy and inpatient services such as acute hospital services, hospice inpatient units and hospice day units [15]. Many patients stay at home during the EOL phase, while being supported by these different outpatient palliative care services. The majority of brain tumor patients opt for community-based nursing facilities, rather than being admitted to hospice care. However, in case of acute medical problems, patients may inadvertently be admitted to acute hospital services [15]. Other reasons for admission to inpatient palliative care units were insufficient symptom control, caregiver distress, social issues and functional and cognitive deficits [8,15].

The lack of symptom control often leads to rehospitalization and transitions between health-care settings, with an increase of healthcare costs and worsening of a patient's QoL as a result. In Italy, a palliative home care program was implemented in primary brain tumor patients to determine its effect on the rehospitalization rate in the last 2 months of life. In addition, the cost-effectiveness of this program was assessed [33]. Compared with a group of brain tumor patients not assisted at home, the hospital readmission rate in the last months of life, the median time spent in the hospital and the costs were significantly lower in the group of patients who participated in the palliative home care program. These home care models may therefore represent an alternative to inpatient hospital care. Although it is expected that these home care models will improve satisfaction with care and the patient's QoL, the exact impact of such a program remains to be determined.

Another important issue regarding the organization of care is the place of death. The place of death varies greatly among countries, likely to be reflected by differences in the organization of healthcare and the accessibility to palliative care services. In a study conducted in The Netherlands, 66% of the HGG patients died at

home, 17% in a hospital, 8.5% in a hospice setting and 8.5% in a nursing home [3]. In Italy, a similar amount (65%) of HGG patients died at home [13]. In Anglo-Saxon regions on the other hand, most brain tumor patients died in a hospice setting (30–68%) [15,26,34] followed by dying at home (16–34%) [15,26,34], in a hospital (13–20%) [15,34] or in a nursing home (2–13%) [15,26,34]. In Austria, most (46%) of the patients died in a hospital, 40% at home and 12% in hospices [2]. HGG patients dying at their preferred place of death, died significantly more often with dignity according to their relatives. According to their relatives, Dutch HGG patients dying at home, died more often with dignity (83%) than patients who died in a hospice (71%), in a hospital (63%) or in a nursing home (50%) [35].

Not knowing a patient's preference on EOL care or care inconsistent with this preference are factors associated with higher healthcare costs [36]. In addition, less transitions between healthcare settings in the EOL phase and dying at the preferred place of death have found to be associated with a dignified death [35]. These results imply that expressed preferences (by means of ACP) on organization and place of care and death could potentially result in reduced healthcare costs, a higher satisfaction with care and a more dignified dying process. This requires timely discussion by the physician with the patient and caregivers.

Caregiver burden

In primary brain tumor patients, the disease also has a large impact on the everyday life of their caregivers. In the majority (67%) of the cases, the partner is the caregiver of the patient. Other caregivers include children, parents, friends or siblings [15]. Overburdening of the caregiver is significantly more often reported in primary brain tumor patients compared with patients with systemic cancers (74 vs 52%, respectively) [8]. Poor cognitive and physical functioning and personality changes, which are frequently occurring in brain tumor patients, are associated with high caregiver distress. Managing relationships and taking care of the patient may cause caregivers to feel exhausted, angry, anxious, depressed and isolated [37]. In the EOL phase, Austrian caregivers of patients diagnosed with glioblastoma frequently reported sadness (90%), fear (69%), burnout (60%), loss of interest in others (54%) and irritation (42%) [2]. Besides these physical and emotional strains, caregivers also report

social and financial problems [38]. In the previously mentioned Austrian study, 29% of the caregivers had financial difficulties, mainly due to job restrictions (50%), and this was associated with a reduced QoL [2].

The risk of overburdening of caregivers of patients with a primary brain tumor emphasizes the need for support. However, caregivers are not always able to access and benefit from supportive care services. Although counseling services are usually available, they were only attended in 8–18% of the cases [15,34]. In addition, hospice day services were only attended in 24%, although these services might significantly relieve distress of the caregivers [34]. Moreover, both caregivers and patients desire information on the disease and the disease trajectory. Even though the treating physician is the most trusted source of information, time spent with the physician is often limited and caregivers questions frequently remain to be unanswered [38]. In Austria, 29% of the caregivers of glioblastoma patients felt insufficiently informed about their tasks and the patient's illness [2].

Healthcare professionals should therefore identify the range of support services that are available to provide the patients and their caregivers with information and a support plan for the complete illness trajectory of the patient, from diagnosis till the EOL. One study showed that caregivers benefit from intensive contact with a specialist nurse [39]. Another option is a support group for caregivers. In the USA, a group intervention for caregivers was implemented with the intention to provide caregivers emotional support, education and information on the disease and care of the brain tumor patient. This group intervention was found to be helpful and was highly appreciated by caregivers [37]. Alternatively, an individual intervention including psychotherapy and cognitive behavioral therapy was found to maintain a stable level of health-related QoL in caregivers of HGG patients, and to improve feelings of mastery (a combination of the caregiver's self-perception and the actual ability to provide care to the patient) [40]. Potentially, internet forums may also provide support for caregivers, because they provide the option to share experiences with other caregivers [39]. Moreover, bereavement in caregivers already starts when the patient is still alive and it is experienced as helpful when patients and caregivers are involved in this bereavement process together, by making funeral arrangements, a living will and seeking for information on what to expect in the last days before death [41].

Conclusion & future perspective

All patients with a malignant glioma will be confronted with incurability in due course and will enter the EOL phase. The main goal in this EOL phase is to maintain the QoL of patients through prevention and relief of suffering. Relief and prevention of both general and disease-specific symptoms are described in several guidelines. Moreover, patients will be confronted with medical EOL decisions such as nontreatment decisions, palliative sedation and physician-assisted suicide or euthanasia. In practice, however, these decisions are often not made (early enough), driven by cultural, legal and religious issues. To optimize palliative care, patients should be involved timely in EOL decision-making. One method to achieve this is with ACP. Although current ACP

programs have proven to be effective in improving the quality of care and QoL of noncancer patients, this approach can and should be optimized for cancer patients. Ultimately, the goal of ACP is to improve the quality of care and QoL of glioma patients as well as their caregivers.

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