



Palliative care in adults with glioma

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Provenance: This is a Guest Editorial commissioned by Editor-in-Chief Xi-Hua Liu, MD (Chinese Research Hospital Association, Beijing, China).

Comment on: Pace A, Dirven L, Koekkoek JA, *et al.* European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma. European Association of Neuro-Oncology palliative care task force. *Lancet Oncol* 2017;18:e330-40.

Received: 08 August 2017; Accepted: 13 August 2017; Published: 01 September 2017.

doi: 10.21037/arh.2017.08.07

View this article at: <http://dx.doi.org/10.21037/arh.2017.08.07>

Gliomas are belonging to the primary brain tumors and are the most common primary malignant brain tumors in adults (1). Although relatively rare, they cause significant mortality and morbidity. Glioblastoma, the most common glioma histology (~45% of all gliomas), has a 5-year relative survival of ~5% (1). Due to the nature of gliomas, the clinical spectrum of symptoms is broad. Disease trajectories may differ from other tumor entities outside the brain in cause of absence of systematic metastasis affecting other organ systems. Functional impairment is mainly elicited through the localisation, size and surrounding oedema. This may include neurological deficits like paresis, aphasia or symptoms like epilepsy or headache, leading to mood and behavioural disorders, as well as cognitive impairment. Increasing brain swelling is consecutively evolving to cerebral herniation with decrease of vigilance and is most frequently the cause of death.

The WHO definition of palliative care states: “Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” (2).

This approach seems especially relevant in the case of patients and families facing the diagnosis of glioma, as symptoms can be manifold and wearing, for all who are involved in care. Early integration of palliative care was reported to have longer duration of survival (3) in patients with lung cancer. Studies demonstrating this effect also in patients with glioma are lacking, but improvement of

quality of life and best possible symptom control should be standard, despite of any disease specific antitumor treatments.

Hereby the study of Pace *et al.*, 2017 publishing the guidelines for palliative care in adults with glioma of the European Association for Neuro-Oncology (EANO) gives a well-structured and helpful recommendation (4). As method, a systematic review was done to identify relevant literature about palliative care in primary brain tumours in adults. When evidence was scarce, evidence from studies of patients with systematic cancer or formulated expert opinions, to provide evidence based guidelines were used (4). In total 251 studies were included in the review. The review is divided in 3 sections: symptom management, patient and caregiver needs and care in the end-of-life phase.

Symptom management

The section symptom management covers all topics of frequent symptoms caused by gliomas like: pain or headache, epilepsy, venous thromboembolism, fatigue, mood and behavioural disorders, rehabilitation for neurological deficits and cognition. As headache results mostly from tumor growth or surrounding oedema, indicating increased cranial pressure, dexamethason with its decongestant properties, is the preferred drug to use for the treatment of headache. A randomised trial (5) of the use of dexamethasone in brain tumours showed that 4 mg/day dexamethasone resulted in the same degree of improvement as a dose of 16 mg/day dexamethasone after 1 week of treatment in patients without signs of impending herniation (4).

Regarding treatment of symptomatic seizures, alternative routes of anti-epileptic drug administration need to be considered when patients with glioma who have a history of epilepsy develop swallowing difficulties; the preferred route of administration depends on the local availability of anti-epileptic drugs and the place of care (4). Here prophylactic treatment with buccal clonazepam and acute seizure treatment with intranasal midazolam are mentioned (6). Furthermore subcutaneous application of levetiracetam or lacosamide are possible “off-label” alternatives (7,8). Benzodiazepines, such as lorazepam or midazolam, are often used as emergency first-line treatment, but the sedating side effects might be undesirable, especially for long-term treatment (8). Prophylactic treatment to prevent from venous thromboembolism is always an individual balance between risk of intracranial haemorrhage and venous thromboembolism with risk of pulmonary embolism. Because the perioperative risk of intracranial haemorrhage increases when prophylaxis is started before induction of anaesthesia, venous thromboembolism prophylaxis with low molecular weight heparin in patients with brain tumours should be started within 24 h after surgery (9,10). Furthermore, no evidence supports extension of primary venous thromboembolism prophylaxis beyond the postoperative period in patients with glioma and the duration of secondary prophylaxis in patients with brain tumours after a venous thromboembolism event should be planned individually, but is lifelong in most patients (4). No evidence could be found of efficacy in the treatment of fatigue in patients with glioma. Nevertheless, as treatments with corticosteroids may be an option in the treatment of headache in glioma, it has been shown in the Clinical Practice Guidelines in Oncology of 2015 (11) that corticosteroids may exert also a therapeutic effect on fatigue (in other tumor entities). However, given the toxicity associated with long-term use, consideration of steroids is restricted to the terminally ill patients with fatigue and concomitant anorexia, and patients with pain, related to brain or bone metastases (11). As the evidence of pharmacological interventions for mood disorders is limited a multimodal psychosocial intervention should be favoured to improve depressive symptoms in patients with brain tumors (4,12). The question of rehabilitation of neurological deficits is in daily practice often triggered by the wish of neurological improvement and the achievement of the “status quo ante”, which might be impossible due to the progressive nature of gliomas. Therefore it is helpful to know, that patients with brain tumors might benefit from

early rehabilitation after surgery as well as rehabilitation after tumor specific treatment (4,13). Moderate quality of evidence exists for medical treatment to prevent or treat cognitive decline and cognitive rehabilitation has only modest positive effects and should be therefore only considered in young patients with relative favourable prognosis (14). Nevertheless, as supportive medication might be a potential cause of cognitive complaints, reduction of the latter should be considered (4).

Patient and caregiver needs

Patient and caregiver needs states separately the quality of evidence for recommendation concerning needs of patients and caregivers. Quality of evidence is very low or low, and consists mainly of need for ongoing support and early integration of palliative and psychosocial support for patients. For caregivers: psychoeducation to increase feelings of mastery, acknowledgement of the caregivers’ role and alleviation of anxiety by more open communication concerning the questions to future death of the patient, might be helpful (4).

Care in the end-of-life phase

The end-of-life phase is defined heterogeneously. For some, it begins with the diagnosis of a life limiting chronic progressive disease, in this study it was defined as the last 3 months and covers the topics of delirium, nutrition, hydration and respiration, advance care planning and organisation of care in the end-of-life phase (4). These are highly relevant themes, as they are often connected with a symptomatic burden for patients as well as for caregivers.

This is especially the case, when delirium occurs. The possible causes and risk factors of delirium are multifactorial and manifold. Actually, a threshold thesis is favoured resulting from a combination of predisposing factors, like age and dementia and additional external factors like e.g., medication or infection, which may result in delirium. Delirium may manifest as hyperactive, hypoactive or mixed forms (15). In case of delirium, the underlying causes must be identified and reacted on (e.g., by adequate symptom control or changes in doses or type of medication) (15). The expert opinion states that if the underlying causes of delirium have been adequately identified and addressed, but delirium could not be relieved, low-dose haloperidol might be recommended as a treatment option in patients with glioma (4). That seems to be a pragmatic approach,

as studies have been shown that olanzapine, risperidone, aripiprazole and haloperidol are equally effective (16) but on the other hand risperidone and haloperidol are not more effective than placebo in the treatment of delirium in patients receiving palliative care and result in more adverse effects (17). Also stated as expert opinion is the recommendation of palliative sedation with benzodiazepines as option in case of refractory delirium (4).

The question of what is still beneficial for patients with glioma, when dysphagia occurs is highly relevant. Treatment decisions about artificial hydration and nutrition are important issues and sometimes discussions are emotional and controversial about benefits. Unfortunately, no studies exist to study the effects of parenteral nutrition and hydration in this patient group. Even if not included in the systematic review of the European association for neuro-oncology of Pace *et al.*, 2017, a multicenter, double-blind placebo controlled randomized trial on parenteral hydration in patients with advanced cancer found, that hydration at 1 L per day did not improve symptoms, quality of life, or survival compared with placebo (18). In the dying phase, the difficulties of swallowing may result in death rattle, due to small amounts of saliva between the vocal cords, a noise which is especially for caregivers disturbing. In a Cochrane review only glycopyrronium reduced significantly the sound of noise, compared to hyoscine. Hyoscine hydrobromide, atropine, hyoscine butylbromide, and octreotide showed in this review no benefits (19).

Advance care planning is a process that supports adults at any age or stage of health in understanding and sharing their personal values, life goals, and preferences regarding future medical care. The goal of advance care planning is to help ensure that people receive medical care that is consistent with their values, goals and preferences during serious and chronic illness (20). Advance care planning can lead to an advance directive, which is a written statement about a person's preferences regarding future medical decisions (4). This is particularly important for patients with glioma due to the nature of disease affecting cognition, communication, and consciousness. One study found a positive association between recorded discussions about prognosis and those about life-sustaining treatments and the presence of a do-not-resuscitate order (21). Apart from the diagnosis of glioma, a randomised trial in older patients who were admitted to a hospital, showed that facilitated advance care planning improved the quality of end-of-life care and patient and family satisfaction, and reduced stress, anxiety, and depression in surviving relatives (22). Due to the rapid

evolution of neurological symptoms, timely advance care planning seems important, especially in patients with glioma.

The organisation of the place of care in the end-of-life phase is influenced by physical and cognitive dysfunction, social issues and communication opportunities in patients with brain tumours. An earlier and integrative approach was found to have a positive effect on the quality of end of life and preferred place of death and was recommended by several studies (23).

Conclusions

The systematic review for development of palliative care guidelines for patients with glioma (4) is extremely relevant and covers the most important topics in the area of symptom management, patient and caregiver needs, and end-of-life phase.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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doi: 10.21037/arh.2017.08.07

Cite this article as: Feddersen B. Palliative care in adults with glioma. *Ann Res Hosp* 2017;1:39.