

Palliative care and quality of life in neuro-oncology

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Abstract

Health-related quality of life has become an important end point in modern day clinical practice in patients with primary or secondary brain tumors. Patients have unique symptoms and problems from diagnosis till death, which require interventions that are multidisciplinary in nature. Here, we review and summarize the various key issues in palliative care, quality of life and end of life in patients with brain tumors, with the focus on primary gliomas.

Introduction

"Palliative care begins from the understanding that every patient has his or her own story, relationships and culture, and is worthy of respect as a unique individual. This respect includes giving the best available medical care and making the advances of recent decades fully available." – Dame Cecily Saunders.

Primary and secondary malignant tumors of the brain, despite combined modality treatment with surgery, radiotherapy, and chemotherapy, are virtually incurable; palliation, maintenance and improvement of the patient's quality of life is of more importance. From diagnosis to the end of life, the care needs of patients with brain tumors are high, underestimated and often neglected. Also, care and needs increase towards the end of life, with a high incidence of neurological symptoms and psychosocial problems [1].

Palliative care, as defined by the World Health Organization, is "an approach that improves the quality of life of patients and their families facing the problems 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". The goal of palliative care is to maximize quality of life, with inputs from a multidisciplinary team to help the patient live as actively as possible whilst neither hastening nor

postponing death [2]. Early integration of palliative care into the treatment schedule improves quality of life and symptom management, and leads to a reduction in aggressive therapy at the end of life [3,4].

Patients diagnosed with brain tumors and their caregivers undergo enormous physical, emotional, social and financial hardships, during diagnosis, treatment and towards the end of life.

Quality of life issues

Quality of life is a concept that encompasses the multi-dimensional well-being of a person in terms of physical or functional status, as well as emotional and social well-being, and therefore reflects an individual's overall satisfaction with life [5]. Health-related quality of life is, by definition, a patient-reported outcome measure, reflecting the patient's perspective.

Studies on quality of life are primarily qualitative and have focused on specific symptoms such as fatigue, sleep disorders, cognitive dysfunction and some symptom clusters. Quality of life in brain tumor patients is complex and multidimensional in nature, with symptoms having interrelationships with each other as well as with patient, tumor, and treatment factors. The increased interest in exploring quality of life as a primary end point for cancer therapy has created a need for prospective, controlled studies to assess baseline and serial quality of life

parameters apart from the classic outcome measures, such as progression-free survival and overall survival [5]. In fact, in the RTOG-0825 study [6], the baseline and early change in neurocognitive function were prognostic for overall survival and progression-free survival. However, assessing quality of life is challenging as validated instruments for measurements are scarce, serial measurements over time are often associated with a lack of compliance, and there is a lack of well-designed trials.

Quality of life measurement

Impairments are the direct consequences of disease, demonstrated by physical examination, and can be evaluated using neurological and neuropsychological examinations. Disability is the impact of this impairment on the patient's ability to carry out activities and can be determined using scales such as the Barthel index, and the Karnofsky Performance Status Scale. Handicap is the consequence of disability on patient well-being; the Modified Rankin Handicap Scale and the Spitzer scale are specific handicap scales for brain tumor patients [7].

Various health-related quality of life measures are available for use in clinical trials as well as in daily clinical work. The European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) consists of 30 items, which are organized into five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), one global health status scale, one overall quality of life scale, and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) [8]. This core questionnaire can be supplemented with a brain tumor-specific questionnaire, the EORTC QLQ-BN20, which includes 20 items, which are organized into four scales (future uncertainty, visual disorders, motor dysfunction, and communication deficit) and seven single items (headache, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control) [9]. All single item and/or multi-item scales of the EORTC questionnaires are linearly transformed to 0–100 scales. Change in scores of ≥ 10 points on any given scale are interpreted as being clinically meaningful; changes of >20 points represent a very large effect. The Functional Assessment of Cancer Therapy-General questionnaire (FACT-G) consists of 27 items covering four domains: physical, social/family, emotional, and functional well-being [10]. A brain cancer-specific subscale consists of 23 items measuring concerns relevant to patients with brain tumors [11]. The EORTC measures are more focused on functioning and symptoms, while the FACT measures cover more psychosocial aspects of the disease and its treatment. The recent M.D. Anderson Symptom Inventory (MDASI) questionnaire was specifically designed to measure the

severity of symptoms in cancer patients (13 items) as well as the interference of these symptoms with activities of daily living (six items) [12]. In addition to the core questionnaire, a brain tumor-specific module (MDASI-BT) has been developed, consisting of nine items (weakness, difficulty in understanding and speaking, seizures, difficulty concentrating, vision, change in appearance, change in bowel pattern, and irritability) [13].

Proxies or health care professionals can rate patient quality of life, when patients are unable to self-report. Proxies and health care providers tend to report more health-related quality of life problems than do patients themselves and proxy ratings tend to be more in agreement with patient physical health-related quality of life domains than with psychological domains [7].

Specific symptoms

Brain tumor patients deal with a significant symptom burden. Studies that have evaluated specific symptoms affecting quality of life have been mostly descriptive, and most examine a heterogeneous group of patients receiving different therapies at different stages of their illness. Most of these studies have focused on fatigue, sleep, pain, seizures, mood disturbance and cognitive function [14–16]. While some of these symptoms are seen in patients with other malignancies, fatigue, neurological deficits, seizure, cognitive dysfunction and mood disturbances are specifically encountered in neuro-oncology.

Fatigue is one of the significant symptoms in patients with newly diagnosed and recurrent high-grade gliomas and may be more significant a problem when compared to patients with low-grade tumors [17–19]. While seizures are more commonly observed in low-grade glioma patients than in high-grade glioma patients, and are associated with deterioration in multiple cognitive domains, the prognostic impact of seizures remains contentious [20–22].

Mood disturbances, especially anxiety and depression, are commonly noted in brain tumor patients [5]. Depression is one of the most important independent predictors of quality of life and has been shown to have an adverse impact on survival [23,24]. Cognitive functioning has also been extensively studied and reported in brain tumor patients [25–27]. Impaired cognition is seen in patients prior to therapy, after radiotherapy and chemotherapy, as well as in patients with tumor recurrence. In a study, cognitive deterioration was detected 6 weeks prior to radiographic failure [28].

Although symptoms such as anxiety, depression, pain, fatigue, and sleep disturbance have been studied

separately, they are often interrelated and may have a common etiology. Research concerning such symptom clusters in primary brain tumor patients is, however, limited. Pharmacological, non-pharmacological and complementary medicine interventions are being studied to assess their ability to improve cognition and mood disturbances, and hence improve the quality of life [29–32].

Factors influencing quality of life

Quality of life scores depend on various patient, tumor, and treatment-related factors [33]. There may be differential importance of various factors influencing quality of life scores in high-grade gliomas and low-grade gliomas.

Patient factors

Performance status is related to quality of life in patients with newly diagnosed high-grade gliomas [34], with a worse Eastern Cooperative Oncology Group (ECOG) performance score associated with worse overall quality of life. In a study evaluating the factors influencing the activities of daily life, the functional independence and functional activity measurement systems were found to be significantly higher in patients with a Karnofsky performance score of 70 or more and a neurological performance scale of 0 or 1 [35]. Some studies of patients with brain tumors reported higher levels of mood disturbance and lower quality of life scores in women than in men [36].

Tumor factors

Several tumor-related factors like tumor grade, location and laterality have been shown to have an impact on health-related quality of life. Patients with high-grade gliomas experience worse quality of life than patients who have low-grade gliomas [7,37]. Depression may also be more frequent in patients with left-hemisphere tumor high-grade gliomas, while right-hemisphere primary brain tumor patients may have higher anxiety. Low-grade glioma patients with lesions in the frontal lobe or lesions in the temporo-parietal lobe are known to have mood disturbances. Also, greater cognitive disability has been noted in those with tumors in the dominant hemisphere [18,38].

Treatment factors

Treatment modalities like surgery, radiation, chemotherapy and concomitant medications can affect the overall quality of life of brain tumor patients. In high-grade glioma patients, those only undergoing biopsy have worse quality of life than those who have undergone gross total resection [39]. Both radiation-induced fatigue and cognitive dysfunction are known to adversely affect quality of life. Also,

cognitive functioning is significantly more impaired in patients receiving whole brain irradiation compared to partial brain irradiation [40]. Patients receiving temozolomide develop more symptoms such as vomiting, anorexia, constipation, and decreased social functioning; the quality of life in newly diagnosed glioblastoma patients receiving either radiotherapy alone or radiotherapy with concomitant and adjuvant temozolomide was substantially impaired compared to historical controls, but no significant decrease in overall quality of life was noted throughout treatment [15].

Bevacizumab, an anti-vascular endothelial growth factor (VEGF) inhibitor, has been studied extensively in recurrent and newly diagnosed glioblastoma patients. In the AVAglio study [41], in addition to significantly prolonging progression-free survival and decreased corticosteroid dependence, bevacizumab was also found to improve or stabilize health-related quality of life compared with placebo; while in the RTOG-0825 study [6], the visuomotor measure of executive function was worse in the bevacizumab arm than the placebo. The contrasting findings related to quality of life between these two large randomized trials could be due to the different parameters evaluated, statistics involved in analysis, and the level of participation in the testing.

Antiepileptic drugs and steroid medications are commonly prescribed to brain tumor patients and can adversely affect physical, emotional, and cognitive functioning. Antiepileptics have been associated with cognitive dysfunction and steroids have been linked to depression in high-grade glioma patients [20,42].

Quality of death and end-of-life issues

When the patient's condition declines due to tumor progression, and further tumor-directed treatment is not an option, the end-of-life phase begins. During this phase, symptom burden becomes high and patients are often troubled by seizures and deficits in cognition, communication, and motor function. Furthermore, loss of consciousness, cognitive disturbances, communication deficits, and confusion often hamper the patient's competence to participate in end-of-life decision making [43,44].

The goal of end-of-life care is to achieve a death with dignity. The intrinsic dignity of every human being is based on their sense of worth, personal goals and social circumstances; personal dignity can be influenced by various factors such as symptom distress, acceptance of disease, level of independence, spiritual well-being, preservation of social role and social support [45]. A recent study found that "death with dignity" was associated with better communication, especially regarding prognosis,

and patients being prepared for death. It was also associated with greater satisfaction with the physician providing end-of-life care on the part of relatives [43].

In order to allow the patient to experience a peaceful death, specific palliative interventions are required for the control of pain, confusion, agitation, delirium or seizures. The lack of control of symptoms can often lead to re-hospitalization with a resultant increase in costs and a worsening of patient's quality of life. In a study of over 5000 patients with glioblastoma, more than one fifth were found to be hospitalized for at least 25% of their remaining lives [46]. Although, hospitalizations are primarily aimed at identifying correctable causes and reducing the symptoms, it may also be emotionally and financially counter-productive; this is true especially in advanced cancer, where hospitalization has been shown to be associated with a reduced quality of life [47]. Many patients prefer to die at home and, in a study on high-grade glioma patients, less than 5% of patients were actually in favour of hospitalization near the end of life [48]. With effective home-based palliative care, the rate and cost of hospitalization can be significantly lowered [49].

Management of symptoms

The main goals of palliative care and end-of-life care in patients with brain tumors are to offer adequate symptom control, relief of suffering, to avoid inappropriate prolongation of dying and to support the psychological and spiritual needs of patients and families [50,51].

Epilepsy appears to be one of the more frequent symptoms in the last stage of disease and represents a major issue in the management of dying patients, particularly in those assisted at home. Loss of seizure control in the end-of-life phase may influence the quality of life of patients and their caregivers. In a recent study on high-grade gliomas, more than 35% of patients developed seizures in the last month before death, with the risk higher in patients with a previous history of epilepsy [52]. Most patients may encounter swallowing difficulties when taking anticonvulsants orally, due to dysphagia and disorientation, hence anticonvulsant therapy needs to be optimized; alternate routes of drug administration (such as intramuscular, rectal, trans-dermal, or subcutaneous) can be considered.

Agitation and restlessness together with physical pain are common features and require appropriate treatment. In the large majority of patients, headache is due to increased intracranial pressure, and usually responds to steroid treatment. In patients with meningeal syndrome due to meningeal involvement, headaches may be severe; steroids, pain medication with non-opioids or opioids might be indicated [53].

In the last weeks of life, most patients experience a progressive loss of consciousness, lethargy, and confusion, and the majority of patients enter into deep coma in the last days. Agitation, delirium and confusion without a complete loss of consciousness may be very distressing for patients and their families, especially in a home care setting. Palliative sedation is the intentional lowering of the level of consciousness of a patient in the last phase of life by administration of sedatives. The objective is to relieve severe physical or psychological suffering that is otherwise untreatable. A subcutaneous infusion of midazolam is used for continuous sedation, if feasible; otherwise intermittent administration of midazolam, diazepam, lorazepam or chlorpromazine may be considered [54].

In the unconscious dying patient, difficulty in clearing upper airways leads to an accumulation of respiratory tract secretions. This "death rattle" may be very distressing for the family and caregivers but is unlikely to be distressing for the patient, owing to the decreased level of consciousness. Gentle nasal suction, postural drainage and administration of anti-cholinergic drugs can help in reducing these symptoms.

End-of-life treatment decisions

End-of-life treatment decisions in neuro-oncology include withdrawing or withholding of medications, nutritional support and palliative sedation. While withholding medication is a planned decision not to undertake symptomatic therapy that is otherwise warranted, withdrawal is the discontinuation of symptomatic treatments, and terminal sedation is defined as the pharmacologically induced reduction of vigilance up to the point of the complete loss of consciousness, with the aim of reducing or abolishing the perception of symptoms that would otherwise be intolerable [53,55]. The process of end-of-life decision making is complicated by the presence of cognitive deterioration that may affect patients' competence to express treatment preferences. Therefore, it is of paramount importance to plan and discuss end-of-life decisions in advance with the patient and the family.

Diversity amongst countries, professionals and cultures

In many parts of the world, hospice and palliative care is still non-existent or in its infancy. Approximately one million individuals die each week around the globe and, even in developed countries, medical services have often focused on preventing death rather than helping people suffering from pain, discomfort and stress [56].

The International Observatory on End of Life Care (IOELC) reviewed and compared the hospice-palliative

care activity in various countries. The countries were placed in six different groups based on their activity: no known hospice-palliative care activity, capacity building activity, isolated and generalized hospice-palliative care provision, countries where hospice-palliative care services are at a stage of preliminary integration into mainstream service provision, and countries at a stage of advanced integration into mainstream service provision. In 2006, 115 of the world's 234 countries (49%) had established one or more hospice-palliative care services. The trend increased by 9% in 2011: 136 of the world's 234 countries (58%) had one or more hospice-palliative care service established. In 2006, 156 countries (67%) were actively engaged in delivering a hospice-palliative care service or developing the framework; by 2011 there had been a slight increase in this number to 159 countries. Also, in most regions of the world, a strong association exists between palliative care and human development, with the more developed countries in the process of integration of palliative care services [57,58].

This heterogeneity across the various countries is highlighted in the study by the Economist Intelligence Unit's research team, which devised the Quality of Death Index by collating data across 40 countries from interviewing various health professionals. The index used differential weightage for basic healthcare environment, availability, quality and cost of end of life care perceived amongst these countries. The bottom-ranked countries in the Quality of Death Index included developing countries, such as China, Mexico, Brazil, India and Uganda, and, surprisingly, some developed countries like Denmark, Japan, Italy, Finland and South Korea. The report also noted that the public awareness regarding end-of-life care was found to be lacking in both developed and developing countries alike [59].

Strong taboos against talking about death exist in various cultures and communities. Even in India, where death is discussed more openly as the inevitable consequence of life, the protective attitude of the relatives still presents a big barrier to open communication with the patient. In the case of children, these taboos around death and dying are stronger. Death of children is more accepted in developing countries with high infant mortality rates, but in the developed world, the "cure at all cost" attitude of the health care professionals and parents heavily influences the end-of-life care. This ideological difference owing to specific cultures was evident when we conducted a survey amongst various neuro-oncology professionals in Asian countries; we noticed that most health care professionals refer patients only when they develop symptoms that require palliation, and the referral of patients to hospice care at the end of life was done rarely [60].

A government-led national palliative care strategy exists in very few developed countries. While government policy statements do not necessarily guarantee quality and availability of end-of-life care, they can be valuable if backed up by the development of strategic services. According to the World Health Organisation, about five billion people have insufficient or no access to medications to control severe or moderate pain. While legally any physician can prescribe opioids for pain control, their availability is a major concern in many countries, essentially because of the complex narcotics laws restricting the sale of morphine, as governments are concerned about illicit drug use [59].

Caregivers' perspective

The diagnosis of a brain tumor has a catastrophic effect not only on the patient but also on the family members. Family caregivers provide extraordinary uncompensated care involving significant amounts of time and energy for months or years, requiring the performance of tasks that are often physically, emotionally, socially, or financially demanding. They are constantly challenged to solve problems and make decisions as care needs change; because the focus is on the patient, their own needs are often neglected [61].

For parents, the grieving process starts right at the diagnosis of the brain tumor and the decision to move toward palliative care is a difficult one, filled with many highly charged emotions including anger, and a search for answers, the intensity of which differs between family members. The neurologic deterioration that characterizes the dying trajectory of children warrants the need for increased awareness of the distinct issues in the palliative care of children with brain tumors and for early anticipatory guidance provided for families. In one study [62], parents described the loss of the ability to communicate as a turning point that led to acceptance. Parental coping mechanisms included striving to maintain normality, and finding spiritual strength through hope and the resilience of their child. Parents are also required to handle routine tasks while learning new skills, involving hands-on patient care, and their stress is compounded by financial hardships, and inadequate community support. Parents of dying children have an overwhelming feeling of loss during the end-of-life phase, and part of the purpose of palliative care is to help them come to terms with the loss of their child. This process is a gradual relinquishing of the instinct to preserve the child's life regardless of their condition and accepting inevitable loss. A perceived loss of control by the parents makes this process a major challenge. However, parents who make this transition are more receptive to their child's needs [63].

Conclusion

In summary, with growing awareness amongst clinicians regarding the quality of life, even in patients with as difficult a disease as brain tumor, focus is shifting towards meaningful prolongation of life. This in turn necessitates an active participation of the patient, family and caregivers, with the health care professional involved in every step of the disease management. "Quality of death" is a concept that could be viewed as a natural extension of quality of life. With the amalgamation of these concepts into routine clinical practice, the basic "right to a decent life" is fortified.

Abbreviations

EORTC, European Organization for Research and Treatment of Cancer; FACT, Functional Assessment of Cancer Therapy; MDASI, M.D. Anderson Symptom Inventory.

Disclosures

The authors declare that they have no disclosures.

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