

Neuro-oncology and palliative care: a challenging interface

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Patients with high-grade gliomas almost invariably develop disease progression despite recent advances in anticancer therapy. Increasingly, the value of formal palliative care consultation and management has been recognized in both cancer and noncancer medicine. However, there is a paucity of data to definitively guide the provision of palliative care for neuro-oncology patients.

This paper aims to review the existing evidence for and describe the interface between palliative care and neuro-oncology, with a particular focus on glioblastoma multiforme (GBM). We also discuss the role of palliative care in nonmalignant neurologic disease where parallels with neuro-oncology might be drawn.

Glioblastoma

GBM remains an uncommon diagnosis. However, for those patients and carers affected, it is life-changing from first diagnosis. The median overall survival for patients receiving GBM therapy is 14 months, and fewer than 10% of patients are alive at 5 years following diagnosis.^{1,2} Further, patients older than 70 years and/or those with poor KPS may not benefit from current palliative anticancer therapies and can have significantly worse outcomes. Indeed, population-based management surveys document median survivals of <10 months and negligible 5-year survival rates.³ Many clinicians view GBM as having the worst of all cancer prognoses; however, median and long-term survival of GBM patients compare favorably with those of patients with other incurable cancers, such as metastatic pancreatic and metastatic lung.²

GBM results in significant morbidity, which can be challenging for patients and their carers, as well as for

health professionals. Physical symptoms include headache, nausea, vomiting, easy fatigue, and excessive somnolence.⁴ Local tumor effects, depending on site, may result in focal or generalized neurologic problems such as seizure, motor weakness, aphasia, and impaired vision.^{5,6} Mood and cognitive disturbance are common.⁷

A multidisciplinary approach including neurosurgery, radiation oncology, neuro-oncology, and allied health is recommended to optimize treatment outcomes.^{3,4} However, few of these multidisciplinary teams would routinely include palliative care, despite the lack of curative treatment options and significant symptom burden. The palliative care needs of patients with GBM can be complex, with a paucity of published data in this area.^{5–9} Parallels do exist, however, between the needs of patients with GBM and those of patients with other, more common cancer diagnoses and nonmalignant chronic neurologic illness.

Palliative Care and Cancer Patients

Palliative care is defined by the World Health Organization as “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.”¹⁰ Palliative care encompasses symptom control and provision of practical support to patients and their carers—from first referral through terminal care and death and into bereavement.¹⁰

The goal of palliative care is to maximize quality of life, drawing on the skills of a multidisciplinary team to help the patient live as actively as possible whilst neither hastening nor postponing death.^{11,12} Palliative care can play an important role in the management of malignant and nonmalignant conditions, in both inpatient and outpatient settings.^{13,14}

There is increasing recognition that early integration models of palliative care are beneficial, particularly

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when it is provided concurrently with anticancer therapy. A recent landmark study by Temel and colleagues¹⁵ is the first to definitively demonstrate a range of benefits to patients with metastatic non-small-cell lung cancer. Patients were randomized to early palliative care integrated with standard oncologic care or to standard oncologic care alone. Perhaps not surprisingly, there was objective demonstration that early intervention with palliative care services resulted in improved quality of life, improved symptom management, and a reduction in “aggressive therapies” at end-of-life.

Perhaps more surprising was the observation that patients referred at diagnosis for early palliative care intervention had an improved survival outcome of nearly 3 months. This was considered clinically significant as well as statistically significant. The basis for this improvement in median survival is the subject of much ongoing debate.^{16,17} With randomly allocated intervention groups evenly matched for performance status, gender, age, and disease stage, the observation is likely due to improvements in symptom control, quality of life, and mood, as for cancer patients there is evidence of an association between increased symptoms, in particular dyspnea and drowsiness, and shorter survival.¹⁸

A new review¹⁹ of the effectiveness of palliative care consultation within a cancer center highlighted the prevalence of symptoms within a referred general cancer population. Six hundred eleven general cancer patients seen over 3 years had an average of 6 uncontrolled symptoms, including 80% presenting with fatigue and 70% with pain (14% classified as severe pain). Of note, review by the palliative care service resulted in significant improvements in pain, somnolence, and symptom distress scores and overall well-being, in most instances observed within the first few days of consultation.

Two recent systematic reviews have analyzed the effectiveness of palliative care involvement in cancer patients.^{20,21} Despite methodological limitations associated with much of the research in this population, these reviews add to accumulating evidence supporting the benefits that palliative care can offer. Improvements were demonstrated across a range of domains, including quality of life, patient and family satisfaction, and end-of-life care. Higginson and Evans,²⁰ incorporating randomized controlled trials and observational/quasi-experimental studies, reported that specialist palliative care input significantly improved pain and symptom management and reduced hospital admissions. Improvement was demonstrated in a variety of care settings, including home-based, hospital consultation, and specialized inpatient palliative care.

Palliative Care and Nonmalignant Neurologic Disease

There is increasing recognition of the efficacy of palliative care for nonmalignant disease, in particular for management of symptoms of respiratory, renal, and cardiac failure.^{13,14,22–25} Several studies have highlighted the symptomatic burden of end-stage organ failure as

being similar if not more pronounced than that of advanced malignancy, as well as the possible utility of palliative interventions for symptom control.^{23–25}

The literature also reflects increasing recognition of the efficacy of palliative care for progressive nonmalignant neurologic disease. In cases of stroke, motor neuron disease, and amyotrophic lateral sclerosis (ALS), there is marked historical recognition and evidence outlining efficacy of palliative care, due in large part to an absence of meaningful disease-modifying therapies.²⁶ Additionally, the literature supports palliative care for advanced Parkinson’s disease, multiple sclerosis, and Huntington’s disease.²⁷ The role of palliative care in these specific patient populations focuses not only on assistance with patients’ physical care, but on communication among treatment teams and formulation of advanced care plans for mechanical ventilation and artificial feeding.²⁸

Progressive neurodegenerative disorders also confer significant physical, social, and emotional burdens on carers. A recent review of palliative care for ALS documented the difficulties faced by sufferers and their families and highlighted the important role that palliative care can play in the multidisciplinary treatment team in maximizing quality of life.²⁹ In stroke, there is increasing recommendation within established guidelines for the early involvement of palliative care services for those with poor-prognosis intracerebral hemorrhage and/or cerebral infarction.^{30,31}

Despite widely held clinician fears that patients, particularly those without a cancer diagnosis, may be unduly disturbed by referral to palliative care, the evidence suggests that a sensitive discussion and introduction to palliative care need not cause distress.³² A prospective study found that the cohort of 40 patients, half of whom had nonmalignant conditions, were able to independently estimate their life expectancy and did not object to questions about end-of-life care.^{32,33}

Palliative Care and GBM

There are limited data on the symptoms experienced by patients with GBM and their palliative care needs. In a series of 169 patients, 82% of whom had primary brain or CNS tumors (with the remainder having metastatic disease to brain), the most commonly encountered symptoms in the last month of life were dysphagia (85%), drowsiness (85%), headache (36%), seizures (30%), and agitation/delirium (15%).⁹

For patients with end-stage GBM, a palliative care cost-effectiveness study of 141 patients who died during an observation period demonstrated a reduction in need for rehospitalization prior to death for those receiving home-based palliative care of 8.3% compared with 26.8% of those not receiving support, despite a similar median survival time in both groups of 13 and 11 months, respectively. Costs associated with hospitalization per patient dying were found to be substantially different, with those for home-based palliative care

costing 2% of those for nonpalliative care (€517 vs €24 076 per patient hospitalization).²²

One retrospective review of 39 patients with primary malignant glioma (representing 3% of that services' consultations over one year) found a high incidence of physical disability, including poor mobility (77%), limited communication (64%), and hemiparesis (62%), and a high symptom incidence, including headaches (62%), seizures (56%), and confusion (51%).³⁴

Depressive symptoms are common in patients with glioma.^{5-8,35-37} A longitudinal study⁸ of nearly 600 patients found that 15% with malignant glioma in the early postoperative period had depression, with a further 93% describing depressive symptoms. In this study, diagnosed depression rose to 22% at 3- and 6-month evaluations. More recent reviews have found prevalence rates of depression and anxiety of up to 48%.⁷ Mood and behavioral changes have been reported to be associated with tumor location: depression with left-sided³⁵ and frontal tumours³⁶; obsession with left anterior tumors; and anger, indifference, and disinhibition with temporal-lobe tumors.^{35,36}

In a recent review published in this journal, Ford and colleagues⁷ examined the supportive care needs of patients with primary malignant brain tumors and found few studies that met inclusion criteria for review; however, their review identified many unmet needs, particularly in the domains of communication and provision of information, and noted progressive cognitive impairment with disease progression, thereby further hampering communication and decision making. Their study also identified rates of anxiety and depression in carers of up to 40%.

The carers of patients with GBM can bear a heavy physical and mental load and often feel responsible for the patient as he/she deteriorates.³⁸ Erratic emotional behavior has been reported as most distressing for families, in part because they lack the skills and knowledge to manage it.³⁹ A small retrospective study of 29 patients with end-stage GBM found that the most common reason for admission to hospital was immobility causing difficulty in home care, followed by acute clinical deterioration and seizures.⁴⁰

Palliative Care and Other Neuro-oncologic Diagnoses

Palliative care data regarding neuro-oncologic diagnoses other than GBM are even more scant. There is little, if any, study into the role of palliative care in lower-grade gliomas and rarer tumors such as medulloblastomas, ependymomas, and malignant meningiomas, among others. No doubt, the problems associated with the care of patients with GBM apply to other tumor diagnoses, which may bring their own issues. The palliative care approach to adolescents and young adults will likely require particular skills and a heightened level of awareness, as must the approach to infants and children with terminal illness.

The Interface between Neuro-oncology and Palliative Care

Models of palliative care service delivery in developed countries differ, particularly in regard to availability of palliative care services in combination with disease-modifying therapies such as chemotherapy, radiotherapy, and surgery.⁴¹

Australia is regarded as having a palliative care service delivery system with well-established quality and benchmarking measures and outcomes among the world's best.⁴¹ The delivery of palliative care is funded by state health departments, in accordance with national guidelines, and no funding or eligibility restrictions are placed on patients regarding anticipated prognosis, diagnosis, age, or concurrent therapies being delivered.⁴² It is provided by multidisciplinary teams including specialist physicians, nurses, allied health and pastoral care services in hospitals, palliative care units, patients' homes, and aged care facilities.

Victoria is the most densely populated state in Australia, with 5.5 million inhabitants, over 75% of whom live in the state capital, Melbourne. There are 6 major tertiary referral hospitals in Melbourne, with 11 designated palliative care units, each ranging in size from 10 to 30 beds, and 7 community-based palliative care providers,⁴³ who service distinct population areas providing specialist nursing, medical, and allied health care, predominantly with the aim of supporting patients and carers at home until death.

The Royal Melbourne Hospital (RMH) is the main provider of surgical and medical neuro-oncology services in the state.⁴⁴ The RMH palliative care service provides both a dedicated 10-bed inpatient unit, on-site within the acute care hospital, and a consultancy service that receives referrals from all departments within the hospital for management advice on symptom control, terminal care, and complex discharge planning. Care in the home after hospital discharge is provided in collaboration with Melbourne Citymission Palliative Care, a nongovernmental organization funded by the state health program.

The referral service sees more than 1100 patients per year, with 64% referred with cancer diagnoses, of which ~20% are primary brain tumors. The inpatient unit receives 450 admissions per year, the average length of stay being 13 days. Fewer than 2% of these admissions have a diagnosis of a primary brain tumor.

The RMH palliative care service works in close collaboration with the neuro-oncology and wider medical oncology service to deliver seamless care to patients from diagnosis, surgery, and anticancer therapy to death, with shared clinical meetings, symptom management protocols, and, importantly, clinical research (including clinical trials).⁴⁵

Conclusion

While the available data are limited regarding the symptoms experienced by GBM patients at end-of-life, and therefore their palliative care needs, there exists

increasing literature supporting the efficacy of palliative care in other cancers and in progressive nonmalignant illnesses, including a range of neurologic disorders.

Palliative care teams bring complementary expertise in symptom management, communication skills, and practical physical and psychosocial support, both within and outside the hospital environment. With the known consequences of GBM diagnosis, it follows that palliative care should and must become an integrated standard part of best practice neuro-oncologic care.

Further research is essential to define this role, particularly for those who may remain reluctant to involve palliative care due to concerns about raising alarm in

patients and removing hope. This research, in a robust way, needs to further delineate the symptoms experienced and document the palliative interventions that can provide meaningful improvements, as has been done in other areas of cancer treatment.

From existing knowledge, patients with GBM experience a range of uncontrolled symptoms throughout their journey, including pain, seizures, and fatigue, that affect quality of life and may be amenable to improvement by palliative care services. Given the demonstrated benefits of early palliative care integration with anticancer therapies in other cancer diagnoses, the time for robust investigation into palliative care for patients with GBM is now.

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