Top Ten Tips Palliative Care Clinicians Should Know When Caring for Patients with Brain Cancer

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Abstract

The diagnosis of an aggressive, primary brain tumor is life altering for those affected and too often portends a poor prognosis. Despite decades of research, neither a cure nor even a therapy that reliably and dramatically prolongs survival has been found. Fortunately, there are a number of treatments that may prolong the life of select brain tumor patients although the symptom burden can sometimes be high. This article brings together neuro-oncologists, neurologists, and palliative care (PC) physicians to help shine a light on these diseases, their genetics, treatment options, and the symptoms likely to be encountered both from the underlying illness and its treatment. We hope to increase the understanding that PC teams have around these illnesses to improve care for patients and families.

Keywords: brain tumor; chemotherapy; glioblastoma; prognosis; radiation; seizures

Introduction

What the lay public calls “brain cancer” actually encompasses a number of diseases with a wide range of cellular origins with quite variable prognoses. Collectively, these tumors are most accurately termed intracranial neoplasms since meningiomas, the most common benign brain tumor, and central nervous system (CNS) lymphomas do not arise from brain tissue.1 Although primary brain tumors represent only 2% of cancer diagnoses, they are the fourth leading cause of years of life lost to cancer because of their generally poor prognosis and because they are the most common solid tumor in children.2,3

Brain tumors can be thought of as either primary intracranial neoplasms or can occur when cancer cells spread from another location to become brain metastases. Brain metastases are more than twice as common as primary brain tumors and may affect 14% of all people with newly diagnosed cancers, with lung, breast, and melanoma accounting for the majority of brain metastases.4 Among primary intracranial neoplasms, gliomas, which include astrocytomas, oligodendrogliomas, and glioblastoma multiforme, represent 80% of primary malignant brain tumors in adults.2 Unlike most solid tumors that are staged using the tumor/node/metastasis system, primary brain tumors are graded based on malignant cell type and aggressiveness of the tumor using the World Health Organization (WHO) grading system (Grade I–IV). These tumors are not “staged” in the traditional sense since their spread tends to be into adjacent tissues rather than outside the neuraxis.

Although present treatment options have shown only small improvements in the overall survival of primary brain cancer patients, these improvements may be tremendously meaningful to individual patients.5 While prognosis has not changed markedly in the past decade, the diagnosis of brain tumors has changed significantly with new molecular and genetic markers providing significant guidance for treatment, prognosis, and new areas of research.6

Despite the clear impact of brain tumors on patients and their families, there has been little research regarding palliative care (PC) for this population. This is unfortunate given that brain tumors present distinct challenges that are not common in other...
tumors (e.g., focal neurologic deficits, cognitive decline, and personality changes). While care is often provided by a multidisciplinary team (neuro-oncologists, neurosurgeons, and radiation oncologists), these teams rarely include PC. This article, written by a team of neurologists, neuro-oncologists, and PC clinicians, aims to provide a present review of brain cancers with a focus on issues relevant to PC clinicians.

**Tip 1: Most Patients and Families Want a Roadmap and Prognostic Information Although Prognostication Can Be Difficult As New Therapies Become Available**

Since many patients with brain cancer worry that they will have a short survival, it is important to provide a treatment “roadmap” to help patients navigate the course of illness and manage expectations for the future. Importantly, disease-focused treatment options do exist with the Stupp trial published in 2005, showing that the combination of radiation therapy and chemotherapy with oral temozolomide for patients diagnosed with glioblastoma increased the two-year progression-free survival from 4% in the radiation-alone arm to 24% for those given combination therapy. While an improvement over older therapies, cure remains quite rare. Unfortunately, some patients and their families continue to struggle with prognostic awareness, hoping that they are being treated for cure rather than with palliative intent.

Situations do exist in which a sustained remission or cure may be possible. Patients with a WHO Grade II astrocytoma or oligodendroglioma with an isocitrate dehydrogenase (IDH) mutation (see Tip 8 for genetic markers) may experience survival of a decade or more. Patients with primary CNS lymphoma who receive rapid induction treatment with a high-dose systemic methotrexate regimen followed by consolidation can show sustained remission. Finally, in this era of immunotherapy, patients with brain metastases, particularly women with HER 2-positive breast cancer, those with lung cancer harboring the ALK, ROS1, or EGFR mutations, or patients with leptomeningeal carcinomatosis from breast, lung, or melanoma, can experience occasional exceptional responses and prolonged survival.

**Tip 2: Seizures Are Common, Adversely Impact Quality of Life, and Require Treatment with Nonenzyme Inducing Antiepileptic Drugs**

Seizures are one of the most common presenting symptoms of primary brain tumors and one of the leading causes of emergency room visits and hospitalizations. For some patients, seizures can be the most distressing tumor-related symptom. Patients and caregivers are disturbed by loss of independence. Once a patient with a brain tumor has a single seizure, they are considered at risk for recurrent events due to the underlying structural abnormality and warrant therapy with an antiepileptic drug. In patients with brain tumors who have never had a seizure, there is at present no evidence to support prophylactic therapy. Acute treatment of seizures or of status epilepticus should follow institutional protocols and typically involves the use of a benzodiazepine to terminate a seizure and intravenous phenytoin to prevent recurrence.

It is important that treatment in the chronic or outpatient setting to prevent recurrent seizures be specific for the cancer patient. Nonenzyme inducing antiepileptic drugs (levetiracetam, valproate, benzodiazepines, ethosuximide, tiagabine, and zonisamide) are preferred to avoid interactions with chemotherapy, corticosteroids, and experimental therapies. Antiepileptic drug (AED) therapy can exacerbate existing fatigue, sedation, and polypharmacy, and the choice of drug ultimately depends on comorbidities and other medications. The most commonly used drug is levetiracetam due to ease of titration, favorable side effect profile, and metabolism through the kidney. The most common reason for discontinuing levetiracetam is irritability and this drug should be avoided in patients with mood and anxiety disorders. Patients typically need lifelong therapy and, at the end of life, should be transitioned to liquid formulations of antiepileptic drugs or liquid benzodiazepines.

Seizures can be a challenging symptom near end of life. Combination of AEDs is often difficult because of patients’ inability to swallow. It is important to recall that AEDs can be continued by other routes, which may include intranasal, sublingual, buccal, rectal, subcutaneous, or intravenous administration. Rectal, intranasal, buccal, and sublingual application of AEDs can be continued by the patient’s caregiver in the outpatient setting. Intranasal midazolam and buccal clonazepam have been shown to have similar efficacy in a small feasibility study. Diazepam can be administered rectally to prevent and treat seizures, although certain preparations are very expensive. Lorazepam, available as an oral concentrate in nearly all hospices, can be an effective substitute.

**Tip 3: Corticosteroids and Systemic Therapy with Bevacizumab Can Mitigate Symptoms for Patients with High-Grade Glioma But Are Not Without Costs**

The use of corticosteroids to treat cerebral edema is a staple of brain tumor management. Although corticosteroids have the ability to rapidly reduce peritumoral edema and relieve neurologic symptoms, clinicians are often liberal with corticosteroid dosing in brain tumor patients. Because many patients with brain tumors receive high doses of corticosteroids for long durations, significant side effects can develop that can paradoxically lead to deterioration in quality of life. For symptomatic patients, adequate symptom improvement can usually be achieved with starting doses of 4–8 mg of dexamethasone per day; most patients do not require the high doses that are sometimes prescribed reflexively (i.e., 16 mg of dexamethasone per day). In addition, clinicians should attempt to limit the duration of corticosteroid use to the extent possible. A tapering plan can be initiated as soon as there is reason to believe that the patient may not require such a high dose of steroids, such as (i) the tumor is responding to systemic treatment, (ii) postradiation edema is resolving with time, or (iii) the tumor has been removed or debulked surgically.

In the event that a patient with high-grade glioma is unable to be weaned off or decreased to a low dose of corticosteroids, bevacizumab therapy may be considered. Bevacizumab is a monoclonal antibody that binds to the circulating vascular endothelial growth factor and is approved for use in recurrent high-grade glioma in the United States. Although it has never been demonstrated to improve overall survival in glioblastoma,
bevacizumab has a role in select patients for the management of tumor-related neurologic symptoms. Due its antiedema properties, bevacizumab may be used as a palliative medication that can significantly lower steroid doses. However, the treatment is expensive and can lead to significant morbidity in a minority of patients, including intracranial hemorrhage, thromboembolism, and impaired wound healing. Thus, bevacizumab should not be used routinely in asymptomatic patients with progressive high-grade glioma; rather, it should be considered on a case-by-case basis based on the presence of symptoms and steroid dependency.

Tip 4: Although Local Therapies (Surgery, Radiation, Tumor Treatment Fields) Target the Tumor, They Can Lead to Systemic Side Effects

There are a number of therapies that are designed to treat tumors locally. Surgery, typically used to debulk or remove a focal mass, is commonly offered although patient selection can be challenging. Gross total resection (GTR) of WHO Grade II diffuse astrocytoma of the frontal lobe had a significant impact on survival for patients of any age. In patients younger than 50 years, GTR conveyed a survival benefit regardless of tumor location. The value of GTR in glioblastoma patients is less clear, but at least one study showed that there was a stepwise improvement in survival between 78% and 100% extent of resection. Biopsy alone for suspected primary CNS lymphoma is sufficient as there is no clear evidence supporting surgical therapies.

Regarding radiotherapy, most brain tumors are now treated with conformal approaches shaped to the tumor itself. Whole-brain radiation therapy was confined, in the past, to the treatment of patients with brain metastases. The cognitive side effects have led to the near abandonment of this therapy in favor of stereotactic radiosurgery (SRS) approaches. SRS is now the recommended therapy for patients with ≤4 brain metastases.

A new approach to treating glioblastoma uses tumor-treating alternating electric current (TTFields). When worn on the shaved scalp and connected to a portable battery more than 18 hours a day, patients with newly diagnosed glioblastoma or those already treated with concurrent chemoradiation therapy and using monthly adjuvant oral temozolomide therapy experienced a five-month increase in median overall survival. The mechanism of action is thought to be a disruption of microtubules, arrest of mitoses, cytoplasmic blebbing, and cell death. The need to shave all hair, reapply the electrodes every 18 hours daily, carry a battery pack, and wear the device more than 18 hours daily dissuade many patients from the use of this device because of perceived negative impacts on quality of life.

Any of these local therapies may have side effects. Surgical side effects include hemiparesis, aphasia, or cortical neglect if the surgery involves eloquent areas of the brain. Postcraniotomy headache and jaw soreness from the local incision occur frequently. Hair loss and loss of taste from involvement of taste buds can result from radiation therapy and can last for the first six months after completion of treatment. Increased cerebral edema around the tumor during and just after radiation therapy can also produce focal neurologic symptoms consistent with the lobe involved. In the short term, radiation often contributes to increased fatigue and to worsening of neurologic symptoms due to inflammation and brain edema. In the longer term, most patients experience short-term memory loss after exposure to cranial radiation that is likely related to the dose given to critical structures such as the hippocampus. TTFields therapy produces heat over the scalp, occasional open sores that require treatment with steroid cream, sun sensitivity, potential anxiety about appearance, and concerns about unexpected battery alarms.

Tip 5: Lack of Effective Therapies for High-Grade Glioma Can Lead to Patients to Seek Out Clinical Trials

Due to the poor prognosis and general lack of effective treatment options for high-grade glioma, many patients with this diagnosis actively seek and are eager to enroll in clinical trials. Similarly, oncologists caring for these patients are typically keen to match their patients to appropriate trials. Unfortunately, since progressive high-grade gliomas and other brain tumors often result in neurologic deficits and declining performance status, situations can arise in which patients are desperate for a novel treatment but may be more appropriately served by high-quality PC.

Many present clinical trials and experimental therapeutics for brain tumors utilize highly invasive techniques, including direct intratumoral injections of investigational agents, surgical tumor resections, and systemic therapies with the potential for significant side effects. It is important that PC is introduced early in the disease course of brain tumor patients, which may allow for more effective decision making when faced with the sudden, difficult choice between a high-risk clinical trial or transitioning to comfort-focused care.

Tip 6: Headaches, Fatigue, Cognitive and Mood Disturbances Are Common and May Adversely Affect Quality of Life

It has been estimated that headaches occur in greater than 70% of patients with brain tumors and can profoundly impact quality of life. Headaches can be present throughout the course of the disease and may have distinct etiologies. Brain tumor-related headaches may occur due to increased intracranial pressure (tumor growth and edema), postoperative pain, tumor-related treatment (radiotherapy and chemotherapy), medications, or underlying predilection for headache syndromes (tension type or migraine headaches). Headaches related to edema from radiotherapy or tumor growth will typically respond to corticosteroids. However, the majority of headaches experienced by patients are more similar to tension type or migraine headaches and should be approached with typical abortive strategies such as nonsteroidal anti-inflammatories or prophylactic medications if warranted.

Fatigue is common as well among patients with primary brain tumors and is reported by up to 70% of patients at some time during the course of their disease. It is often associated with other complex symptoms such as depression, sleep disturbance, and pain. Although the pathophysiology is complex and poorly understood, it is likely multifactorial in nature and includes the disease itself, disease-related therapies, concomitant medications, and neurological impairment affecting quality of life. There have been no pharmacologic or nonpharmacologic interventions shown to be effective in patients with primary brain tumors, and conventional stimulants such as modafinil, armodafinil, and methylphenidate have not been shown to be superior to placebo in clinical
Table 1. Common Complications of Cytotoxic Chemotherapies Used to Treat Gliomas

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Complications of antineoplastic therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>Rash (temozolomide, procarbazine)</td>
</tr>
<tr>
<td></td>
<td>Delayed wound healing (bevacizumab)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Myelosuppression (chemotherapy)</td>
</tr>
<tr>
<td></td>
<td>Myelodysplasia, leukemia (chemotherapy)</td>
</tr>
<tr>
<td>Infectious</td>
<td>Pneumocystis jiroveci pneumonia</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Bowel perforation (bevacizumab)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Neuropathy (vincristine)</td>
</tr>
<tr>
<td></td>
<td>Stroke (bevacizumab)</td>
</tr>
<tr>
<td></td>
<td>Reversible posterior leukoencephalopathy syndrome (bevacizumab)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pulmonary fibrosis (lomustine)</td>
</tr>
<tr>
<td>Vascular</td>
<td>Arterial thrombotic events (bevacizumab)</td>
</tr>
<tr>
<td></td>
<td>Venous thromboembolic events (bevacizumab)</td>
</tr>
<tr>
<td></td>
<td>Hypertension (bevacizumab)</td>
</tr>
</tbody>
</table>

Trials. Literature from the general cancer population has suggested that aerobic exercise may help mitigate fatigue during and after tumor-directed therapy. Evaluating and treating common causes of fatigue, including pain, emotional distress, medication effect, anemia, sleep disturbances, and neurologic impairment, may be helpful to minimize the impact of fatigue on quality of life.

Depression is another common symptom for those with brain tumors, affecting up to 20% of patients during the course of their illness; those with functional impairment or previous depression are at higher risk. A study of patients with high-grade glioma suggested that symptoms of depression were most common immediately following surgical resection and during the subsequent six months. Furthermore, physician recognition of depression was generally poor, and patients diagnosed with depression experienced more complications and shorter survival. Therefore, systematic screening for depression should be undertaken as part of the comprehensive management of patients with brain tumors. The optimal treatment of depression in this population is unclear as there have been no prospective trials. However, there is evidence in the general cancer population to support psychotherapeutic (e.g., cognitive behavioral therapy) and pharmacologic (e.g., selective serotonin reuptake inhibitors and anxiolytics) interventions.

Cognitive impairment is common in persons affected by brain cancer, including brain cancer survivors, and may be due to the direct effects of the cancer on brain structure or side effects of treatments. Cognitive impairments are important to ascertain from a PC perspective as they may influence goals-of-care discussions and can contribute to diminished quality of life, disability, and caregiver burden. Medications such as acetylcholinesterase inhibitors may provide mild benefit in some patients. Additional support and guidance from speech therapists, occupational therapists, or neuropsychologists may also be considered and can be helpful for some patients and families.

Tip 7: Side Effects from Systemic Therapies Are Common

As outcomes for patients with primary brain tumors remain generally poor, enrollment in clinical trials with novel therapies is encouraged. In the absence of trial options, cytotoxic chemotherapy is part of the standard of care for most patients with glioma. Treatment requires regular laboratory monitoring before and during therapy as well as comprehensive evaluation to mitigate side effects. The most common side effects from frequently used medications are listed in Table 1.

Tip 8: Genetic Markers in Brain Cancer Aid in Diagnosis, Prognosis, and in Predicting Response to Therapy

As with many cancers, our identification and improved understanding of genetic markers in brain tumors have transformed how we classify, prognosticate, and treat these malignancies. The WHO updated its classification of brain tumors in 2016. At present, patients are given an integrated diagnosis that is based on a combination of histologic features and genetic markers.

There are four key markers that influence how we take care of patients: the IDH mutation, the 1p/19q codeletion, the H3K27M mutation, and methyl-guanyl-methyl transferase (MGMT) promoter methylation. Their impact on decision making is summarized in Table 2. The IDH1 and IDH2 mutations are associated with longer survival in gliomas and patients who are IDH wild type have poorer prognosis.

Table 2. Genetic Markers for Brain Cancer Prognosis and Therapeutic Response

<table>
<thead>
<tr>
<th>Genetic marker</th>
<th>Relevant tumors</th>
<th>Effect on prognosis</th>
<th>Effect on therapeutic choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH mutation</td>
<td>All diffuse astrocytic and oligodendrogial tumors</td>
<td>Associated with longer survival</td>
<td>None</td>
</tr>
<tr>
<td>1p/19q Codeletion</td>
<td>Oligodendrogial tumors</td>
<td>Associated with longer survival and tumors may be more sensitive to chemotherapy and radiation</td>
<td>Favors incorporation of chemotherapy and radiation to achieve long-term disease control</td>
</tr>
<tr>
<td>H3K27M mutation</td>
<td>Diffuse midline glioma</td>
<td>Associated with aggressive tumors</td>
<td>None</td>
</tr>
<tr>
<td>MGMT promoter methylation</td>
<td>Glioblastoma</td>
<td>Associated with better responses to alkylating chemotherapy and improved survival</td>
<td>Favors use of temozolomide</td>
</tr>
</tbody>
</table>
independent of histology. The 1p/19q codeletion defines the
diagnosis of oligodendrogliomas; patients with the codele-
tion live longer and its presence predicts response to both
chemotherapy and radiotherapy. The H3K27M mutation
should be tested in patients with brainstem and thalamic
gliomas; it defines the entity referred to as “diffuse midline
glioma,” which is characterized by aggressive growth and no
proven response to chemotherapy. MGMT methylation is an
important biomarker in patients with glioblastoma and pre-
dicts sensitivity to temozolomide and longer survival. In
older patients, where treatment is not clearly defined, the
presence or absence of MGMT methylation can be used to
help clinicians decide whether or not to incorporate temo-
zelomide into the regimen. These markers are increasingly
incorporated into clinical care and decision making.

Tip 10: Patients Lose Decision-Making Abilities Early
in the End-of-Life Phase So Advance Care Planning
Can Help to Facilitate Referral to Hospice
and Ensure Goal-Concordant End-of-Life Care

Patients with high-grade primary brain tumors can have a
high symptom burden throughout their disease trajectory
but this often worsens toward end of life. Major symptoms
that diminish quality of life for patients and their families
near end of life include weakness, cognitive disturbances,
drowsiness, aphasia, and seizures. Referrals of brain tu-
mor patients to PC and hospice happen mostly late and in
the end-of-life phase (median of 28–70 days before death),
when the impact on symptom control and suffering may be
reduced.

Many patients with high-grade brain tumors lose the
ability to participate in end-of-life decision making for sev-
eral weeks before death. Therefore, advance care planning
(ACP) and hospice should be approached earlier in the dis-
ease trajectory. Few studies systematically assess the role of
timing of ACP in patients with brain tumors but it is generally
recognized that it should happen early in the disease as pa-
tients’ faculties to facilitate decision making, such as speaking,
understanding, and processing, decline in the last months of
life.

Caregivers of patients with brain tumors perceive
the planned transition to end-of-life care and hospice as par-
ticularly important, with the hope that their loved ones can
experience a dignified death that is congruent with their
wishes. ACP is associated with lower hospital readmission
rates and decreased intensive care utilization but is unfortu-
nately underutilized in this population.

Conclusion

The introduction of a PC approach to the treatment of those
living with brain cancer, including referral for specialized PC
services, holds significant promise to improve quality of life,
family distress, and coordination of care. There is a need for
neuro-oncologists and other members of the oncology care
team to adopt a PC approach and for palliative medicine
specialists to be aware of the unique needs of this population.
Research is needed to develop empiric PC frameworks,
models, and interventions to better meet the needs of this
population.

Author Disclosure Statement

No competing financial interests exist.

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