Palliative care is a multidisciplinary approach to practicing medicine that addresses symptom management, alleviation of pain, assessment of psychosocial and spiritual distress or suffering, and practical support for patients and their caregivers with a goal of improving quality of life for patients with serious and life-threatening illnesses. Although palliative care has gained acceptance as an important part of comprehensive cancer care at the end of life, early integration of palliative care is less common, despite the scientific proof that patients with cancer who receive palliative care not only live better, but longer. In a landmark study, patients with metastatic non-small cell lung cancer were randomly assigned to receive early palliative care integrated with standard oncology or standard oncologic care alone. Early palliative care was associated with improved quality of life, improved symptom management, reduction of aggressive tumor-directed therapy at the end of life and, improved survival.

Despite extraordinary advances in neuro-oncology most brain tumors remain non-curable. Competent neurologic practice is therefore all about improving the quality of life of brain tumor patients, from diagnosis onward. In 1996, the Ethics and Humanities Subcommittee of the American Academy of Neurology (AAN) recognized the importance of competence in the palliative medicine when it emphasized, "It is imperative that neurologists understand and learn to apply the principles of palliative care as...many patients with neurologic disease die after long illnesses during which the neurologist acts as the principle or consulting physician."

Symptom Management in Brain Tumor Patients
While the primary neuro-oncology treatment is geared to extend life and progression-free survival, there is increasing focus by patients, families, and physicians that maintaining quality of life is as important as increasing survival time. Brain tumors can present with many signs and symptoms that have immediate impact on the patients' quality of life. These symptoms can be either caused by the location of the brain tumor or by oncologic treatment (surgery, radiation, chemotherapy). Proactive symptom management is essential to maintain the patient's quality of life and at the same time to support caregivers and families.

Seizures
Epileptic seizures are common in neuro-oncology and affect 30–80 % of all patients with brain tumors. Seizures can be potentially life threatening and can cause significant morbidity especially in patients with otherwise controlled tumors. The seizure frequency is generally higher in patients low-grade glioma (WHO grade II) (60–80 %) and less prevalent in glioblastoma (WHO grade IV) (29–49 %). Approximately 40 % of brain tumor patients present with a seizure as a first symptom and these patients remain at an increased risk for recurrent events despite treatment with antiepileptic drugs. The use of antiepileptic prophylaxis for glioma is currently not recommended for patients who have never had a seizure. Despite good seizure control during treatment, up to 86 % of patients suffer from seizures at the end of life. Seizures in the end-of-life phase have been associated with non-peaceful death. The optimization in this setting can be challenging as many brain tumor patients are unable to swallow or to take oral medications due to changes in mental status. If oral or intravenous application is not appropriate, seizure medications can be supplied intramuscularly, subcutaneously, rectally, or via buccal or intranasal application. Diazepam especially can be delivered as rectal suppository and the buccal or intranasal application of midazolam has also been shown to stop seizures.
Fatigue
Many patients report severe impairment due to fatigue throughout the course of the disease, but it is most prevalent around the time of radiation treatment. The underlying mechanism for cancer-associated fatigue remains unclear, but factors associated with higher risk for fatigue include older age, female sex, decreased performance status, and treatment-related factors. Fatigue has significant impact on patients physical, mental, and emotional functioning. Forty-two percent of patients with primary brain tumors report their energy levels to be “quite a bit low” or “very low” at some point in their treatment course. One prospective study found that one-third of patients with brain tumors had clinically significant fatigue at baseline, prior to starting radiation. Further, fatigue is an independent predictor of overall survival. The NCCN guidelines for clinical practice recommend physical exercise as first-line treatment for cancer-related fatigue. The use of stimulants such as methylphenidate and modafinil has been evaluated in several studies for brain tumor patients, but results are overall inconclusive.

Depression and Cognitive Dysfunction
The quality of life of the patient with a brain tumor may be largely dependent upon the competence in palliative care of the care team. Distress in patients with newly diagnosed brain tumors may be manifest by severe anxiety and/or depression and the risk of emotional upset is highest among patients with a premorbid mood disorder. Patients with anterior frontal tumors may have a higher risk for depression than those with tumors in other locations. Depression and anxiety are negatively associated with quality of life, and there is a weak association between depression and reduced survival. Based on evidence in other seriously ill patients and cancer patients, selective serotonin reuptake inhibitors (SSRIs) should be considered as first-line therapy for treatment of depression and anxiety in glioma patients.

Cognitive deficits in adults with brain tumors have been reported at rates of 29%-90%. The etiology of cognitive impairment in patients with brain tumors is often multifactorial and may include the tumor itself, seizures, metabolic disturbances, along with side effects of surgery, radiation, and/or chemotherapy.

Headache
Approximately 50% of patients with brain tumors experience headache pain, with estimates ranging from 33% to 71%. The first step to treating headache in patients with brain tumors is to identify the reason for the headache. Headache may be due to mass effect, increased intracranial pressure, intratumoral hemorrhage, or transient increases in intracranial pressure known as “plateau waves.” Postsurgical pain may trigger headaches, and patients with a history of migraine may experience resurgence or worsening of their typical headaches. Since the brain itself has no pain receptors, headache in patients with brain tumors may be attributed to several possible mechanisms including traction on draining veins, the middle meningeal artery, skull-based arteries, cranial nerves, pain afferent fibers, inflammation, or inflammatory mediators such as leukotrienes. Primary and adjuvant analgesics such as acetaminophen, nonsteroidal anti-inflammatory medications, and anticonvulsants may be helpful. Opioids are generally not as effective for managing headache as they are for somatic, visceral, or neuropathic pain.

Communication Strategies
For patients with brain tumors, the integration of palliative care early into standard neuro-oncologic care is especially important, given the profound and often early losses in language Function, changes in personhood and decision making capacity. Based on these neurological deficits, it has been suggested to address advanced care planning early during the disease trajectory. Hope is fostered through the assessment and management of symptoms and the assurance of non-abandonment offered by the treating neuro-oncologist. The “Ask, Tell, Ask” method is a tool for effective communication in which the doctor first asks the patient what he or she knows, wants to know, or is concerned about, then delivers the information, then checks the patient’s understanding of the information that was provided. Utilizing other paradigms such as the SPIKES protocol for breaking bad news assures that doctor-patient communication is effective, patient-centered, sensitive, empathic, and compassionate.

Table 1. The SPIKES Protocol for breaking bad news or giving important medical information
S: SETTING and listening skills
P: Patient’s PERCEPTION of condition and seriousness
I: Invitation from the patient to give information
K: Knowledge – giving medical facts
E: EXPLORE emotions and EMPATHIZE as the patient responds
S: STRATEGIZE and SUMMARIZE

The Empathic Response is a skill, not a feeling. It is not necessary for the clinician to have the same feelings as the patient nor to agree with the patient’s view or assessment. What is necessary is that the patient feel validated and understood. Empathy is best communicated as follows:
1) Identify the Emotion
2) Identify the cause/source of that emotion
3) Make the connection between #1 and #2.

For example, “I can see how sad this news makes you feel. It must feel awful.” Listening to patients and families is one of the most important tools a clinician may employ in assuring validation and a compassionate response. Best listening strategies include:
   a) Ask open-ended questions (e.g., Ask “How did you feel when that happened?” vs. “You felt awful, right?”
   b) Tolerate silence. Ask, “And you father…?” vs. “When did your father die?”
   c) Use a word from what the patient has said, (e.g., “You use the word embarrassing. Tell me more…”)

Word choice may be helpful or may widen a potential gap between clinicians and patients and families. Consider the potential negative impact of the following questions or statements:

--Do you want to be aggressive?
--Do you want to have everything done?
--It's time we talk about pulling back.
--I think we should stop fighting
--Your husband FAILED all of the chemotherapy we provided.

One of the barriers toward delivery of palliative care has been the unfortunate association with palliative and LESS care. Clinicians must never associate palliation or hospice with doing LESS for patients and families. The conversation must shift from doing “everything” vs. doing Less toward a more helpful discussion of a shift in the goals of care.

Some more helpful language might include:
--I want you to know that no matter what happens with your disease, I am here. I will always do my best. You will always be my patient.
--Even if we decide together to stop treating the cancer, I will never stop treating YOU.
--The chemotherapy failed (not the patient!) to provide the response we had been hoping for together. Let's talk about other strategies and what is most sensible now.

Palliative Care Needs At or Near The End of Life

Agitation and Delirium
Throughout much of the course of the disease, palliative care for patients with brain tumors focuses on maximizing cognitive function and minimizing fatigue. Among atypical antipsychotics, quetiapine and olanzapine are often used for agitated delirium or insomnia. For patients unable to swallow pills, haloperidol in an injectable form may be preferred.

Under some circumstances in patients who are imminently dying, sedation may be an important tool for minimizing suffering. Opioids may be used for control of pain or dyspnea, while benzodiazepines and neuroleptics are often added for agitation and delirium (see Table 3).

Established legal, ethical, and palliative care guidelines support the use of sedation for patients who are imminently dying to assure comfort and dignity as a last resort. In studies of sedation in the setting of either home or inpatient hospice, there was no difference in the patients’ time to death when comparing those who were sedated and those who were not, underscoring the importance of reminding family and loved ones that sedated patients die not from the prescribed sedation, but from the end stages of their disease.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route</th>
<th>Starting Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>p.o. i.v. i.m.</td>
<td>2.3mg/day bid-tid</td>
</tr>
<tr>
<td>Diazepam</td>
<td>po, Pr, Iv. Im</td>
<td>2.10mg bid-tid</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>po, ODT</td>
<td>0.5mg bid-tid</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>po, ODT, im</td>
<td>2.5-5mg qhs</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>po, im, iv</td>
<td>0.5-1mg every 1-4 hrs, prn</td>
</tr>
</tbody>
</table>

Management during the end of life phase

Patients who are dying from a serious illness often go through stages of grief, loss, and denial. Patients’ central concerns often revolve around families and relationships, the patient/s own psychological integrity, and finding meaning in life. There is an opportunity at the end of life to enhance relationships and leave a legacy. In order to meet these challenges, mental distress and suffering must be well controlled.

Near the end of life, the neuro-oncologist must be able to recognize that the patient is dying and advise family and caregivers. In most patients with primary brain tumors, the cause of death is brain herniation due to tumor progression. In a minority of patients, death may be due to complications of the tumor including seizure, intracranial hemorrhage, infection, or pulmonary embolism. Rarely, death may occur due to treatment complications such as bowel perforation from steroids. Understanding how patients with brain tumors die and preparing family and friends about what to expect can ease anxiety and be very helpful to grieving loved ones as they prepare for the inevitable end of life.

A diagnosis of brain tumor impacts the whole person: mind, body, spirit, and the patient’s primary relationships. Early integration of palliative care and competency in communication skills may help to lessen the emotional blow of the initial diagnosis and set more realistic expectations for the course of treatment. The emerging practice standard for neuro-oncologists now includes competency in palliative care. Patients and families should expect their doctors to emphasize quality of life as an essential part of delivering the highest quality of care. Neuro-oncologists must be expected to treat the patient, not only the tumor, from diagnosis to bereavement.

Comprehensive care of patients with brain tumors requires mastery of symptom management, communication techniques, knowledge of the results of randomized controlled clinical trials to afford patients the opportunity to live as well as possible for as long as possible.

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