NEURO-ONCOLOGY

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Welcome to the neuro-oncology update. By the end of this presentation you will have an increased understanding of the current management glioma. You will also have an understanding into the approach and treatment of brain metastases. We will also discuss some of the more common neurologic complications of systemic malignancies and their treatments.

GLIOMA

Glioma is a form of cancer born within the nervous system. It is up to the determination of the pathologist as to which cell started growing at an uncontrolled manner. Based on that designation, the tumor is deemed either an astrocytoma or an oligodendroglioma. The WHO has been revised in 2016 and now includes some genetic and molecular markers to assist in making this diagnosis. As such, gliomas continue to be graded 1-4. Grade one is most typically benign and found in pediatrics. Example of grade 1 tumors include pilocytic astrocytoma or SEGA, commonly found in tuberos sclerosis. Grade 2 gliomas could be considered either astrocytic, oligodendroglial, or a combination of both deeming them oligoastrocytomas. A grade 3 glioma maybe an astrocytoma or an oligodendroglioma. In both cases these would be referred to as “anaplastic”. Grade 4 astrocytoma is also known as glioblastoma multiforme (GBM).

Glioblastoma multiforme is a highly aggressive brain cancer requiring aggressive treatment including surgical resection, radiation, and chemotherapy. Even with this aggressive course average survival is approximately 14 1/2 months. GBM tends to occur more commonly in men than women and strikes in late middle age. Prognosis is dependent on age, performance status, and histologic subtype. For older patients with limited functional status, survival may be on the order of several weeks to a few months.

Patients with glioblastoma are often treated with safe surgical resection followed by concomitant chemotherapy (temozolomide-TMZ) and radiation followed by adjuvant chemotherapy(TMZ). Recent data also suggest the implementation of tumor treatment fields, following completion of radiation, which also extends overall survival. Unfortunately this is a disease that is not curable. At relapse the FDA has approved the use of bevacizumab, a monoclonal antibody targeting VE GF. This can be used alone or in combination with lomustine.

Clinical trials utilizing immunotherapy and vaccines are ongoing. None have yet passed the rigor of a randomized double blinded placebo controlled study against the standard of care which is radiation and chemotherapy (temozolomide).

The majority patients with anaplastic astrocytoma or anaplastic oligodendroglioma are treated in the same way we would treat a patient with GBM. The exception in a patient with an anaplastic oligodendroglioma. If the patient is young with a good performance status, and found to have the molecular signature of 1p19q codeletion, consideration is given to utilizing temozolomide chemotherapy in the neoadjuvant setting to attempt to achieve tumor shrinkage limiting the amount of tissue requiring treatment with radiation. Clinical trials are o going looking at a combination of PCV (procarbazine, CCNU, vincristine) versus TMZ for superiority. To date, most clinicians prefer utilizing TMZ to avoid toxicities.

Patients with grade 3 and grade 4 tumors are considered to have high grade glioma. If elderly or frail, rather than the traditional six weeks of chemoradiation, evidence has proven that abbreviated courses of radiation have been found to be just as effective limiting toxicities. In cases where the tumor demonstrates methylation of mgmt (O6 methyl guaninine methyl transferase), treatment with TMZ alone may be considered appropriate.

For patients with low-grade glioma's, surgical resection may improve quality-of-life particularly if the patient has lesion related epilepsy. If the tumor is found to be oligodendroglial and has 1p19q codeletion neoadjuvant TMZ may be worthwhile. If the patient is older and the tumor is larger than 3 cm or an incomplete resection is able to be achieved, this subset of patients would be considered high-risk and should be treated with concomitant chemoradiation followed by adjuvant TMZ.

Patients with a grade one astrocytoma are often cured with surgical resection.

METASTATIC DISEASE

There are at least 170,000 new cases of brain metastases per year. In fact, brain metastases are the most common brain tumor in adults and the most common neurological complication of systemic cancer. The rate of brain metastases is increasing as a result of improved the systemic therapies. 15 to 20% of cancer patients will be diagnosed with brain metastases during life with an additional 20% being confirmed at autopsy. Most patients with brain metastases have lung cancer as the primary. Although melanoma makes up less than 5% of all malignancies, it remains one of the most common causes of brain metastases. Metastatic melanoma is more likely to be multiple whereas brain metastases as a result of renal cell carcinoma tend to be solitary. Histologies within an organ type can exhibit disparate metastatic profiles. For example, inflammatory breast cancer behaves much differently than triple negative breast cancer. Some cancers such a small cell lung cancer, melanoma, and breast cancer can have both parenchymal brain metastases as well as leptomeningeal disease concurrently.

Of the primary tumor types, lung is the most common to metastasize to the brain followed by breast, melanoma, and then G.I. The pathophysiology as to how brain metastases occur is complex. Cell division and growth within the primary tumor itself occurs leading to cellular invasion of local tissues. The tumor then enters into the bloodstream or lymphatic channels and arrests in the microvasculature of the secondary site later invading target tissue. From that point, proliferation of the cancer cell then leads to the site of distant metastasis. In the brain specifically, the cancer cells are thought to aggregate in capillaries that form at the gray white junction. They then interact with endothelium and extravasate into the brain parenchyma. Each metastasis forms an aberrant vasculature causing blood brain barrier permeability. Approximately 80% of brain metastases are found within the cerebral hemispheres. 15% are found within the cerebellum and 5% in the brainstem. Pelvic and G.I. tumors tend to metastasize to the posterior fossa.

Up to one third of patients may be asymptomatic. Some of the generalized symptoms that a patient may experience can be related to increased intracranial pressure such as headache, lethargy, nausea, vomiting, and confusion. Focal symptoms would include hemiparesis, visual field defects, seizures, ataxia, and aphasia. Paraneoplastic syndromes such as SIADH can be attributable to small cell lung cancer, thymic cancer, or melanoma. Some patients may present with signs and symptoms of a stroke or coma. Most commonly this would include melanoma, choriocarcinoma, renal cell, and thyroid carcinoma.

Noncontrast head CT would demonstrate a hypodense lesion in the gray white junction with surrounding edema, mass effect and possible hemorrhage. Contrast enhanced imaging, specifically MRI, would be considered the gold standard imaging technique. One would expect to see a ring enhancing lesion on contrast enhanced MRI. Approximately 75% of patients with intracranial metastases are found to have multiple lesions with 80% of cases having a known primary tumor.

Work up should include contrast enhanced neuroimaging. Consideration should be given to the differential diagnosis of solitary metastasis which can include high grade glioma, abscess, multiple sclerosis, lymphoma, and granuloma. If the primary tumor is unknown, a screening CT of the chest, abdomen, and pelvis should be performed. Tertiary testing should be done as appropriate, including a lumbar puncture, bone marrow testing, mammogram, and testicular ultrasound.

Prophylactic cranial radiation (PCI) is given in cases with small cell lung cancer given the predilection to metastasizing to the brain. The rate of metastasis following treatment for SCLC with systemic therapy is 50% over two years. PCI has been found to provide a 54% relative reduction in new brain metastases. The most common adverse effect associated with PCI is delayed leukoencephalopathy.

As for symptomatic treatment, 20% of patients present with seizures. Antiepileptic drugs that induce the cytochrome P450 system should be avoided and newer agents should be utilized. The AAN practice parameter cautions against prophylactic AED use.

For treatment of cerebral edema, dexamethasone can be dosed from 4 to 16 mg per day. Some of the adverse effects associated with dexamethasone usage include hyperglycemia, osteopenia, G.I. bleed, mania, immune

suppression, and weight gain. Other modalities that can be utilized to treat malignant cerebral edema include surgery, hyperventilation, and osmotic diuretics.

If a patient has a solitary metastasis and a performance status good enough to withstand surgery, surgical resection is recommended. If the patient has 2 to 3 metastases and there is one that is life-threatening, the metastasis that is life-threatening should be resected. Otherwise radiation remains the mainstay of treatment for brain metastases. Stereotactic radiosurgery to the operative cavity or to up to 10 lesions is appropriate. More than that would require whole brain radiation therapy for palliation.

The utilization of chemotherapy for treatment of brain metastases remains complicated. Given the blood brain barrier, only small lipophilic agents cross. Some of the barriers to treatment have been penetrance, resistance, and limited bone marrow reserve as a result of heavy pre-treatment. There are some primary malignancies in which it may be appropriate to consider utilizing chemotherapy. For non-small cell lung cancer, temozolomide and tyrosine kinase inhibitors cross the blood brain barrier. For breast cancer, lapatinib and trastuzumab cross the blood brain barrier although the improvement in overall survival remains unclear. For germ cell tumors with brain metastases cisplatin based regimens may be considered. For melanoma BRAF inhibitors and ipilimumab have been associated with improve survival. Lastly, for renal cell carcinoma VEGF inhibitors such as sunitinib and bevacizumab have been utilized.

94 to 98% of patients with metastases to the spine have vertebral or epidural disease. This can present as intradural intramedullary, intradural extr medullary, or extradural. Intramedullary metastases account for approximately 5% of all patients dying from cancer. There are approximately 25,000 cases yearly in the United States with breast prostate and lung primaries being most common. Renal cell, myeloma, and non-Hodgkin's lymphoma occur with less frequency. The pathogenesis and pathophysiology involves vertebral spread through Batson’s plexus. Arterial emboli as a result of metastases embolizing into the rich vasculature of the bony spine is another proposed mechanism of spinal metastases as well as direct extension.

Thoracic back pain is the most common presenting symptom followed by symmetric weakness and sensory loss. Bowel and bladder involvement parallels weakness. Patient may also present with cauda equina syndrome. Imaging should include plain x-ray followed by bone scan, PET scan, CT scan, or MRI. MRI with and without contrast would be considered the gold standard. The median survival is on the order of six months. If the patient is ambulatory at the time of diagnosis fix the survival is extended 8 to 10 months. If they're not ambulatory at the time of diagnosis survival is limited to 2 to 4 months.

For intradural intramedullary metastases 50% of cases have lung is a primary. Presenting symptoms include pain, weakness, and Brown Sequard syndromes. Opioids and neuropathic pain medications are often required. External beam radiation therapy and corticosteroids are utilized. The role of surgery is limited in intramedullary disease but may be appropriate for epidural disease.

NEUROLOGIC COMPLICATIONS OF CANCER TREATMENT

Radiation therapy is a mainstay of cancer treatment and may be used as definitive therapy if resection is not feasible or in the adjuvant setting. For each tumor subtype, there are specific parameters regarding radiation dose, duration, and volume of treated tissue. Neurologic symptoms can develop during therapy and/or after decades. Based on the area treated, neurologic complications could involve the brain, spinal cord, and/or peripheral nerve. Improvement in overall survival has raised concerns about quality-of-life and extent of radiation induced deficits. Some of the complications that can occur in the brain include acute and delayed leukoencephalopathy, cerebral atrophy, and cognitive changes. Growth and endocrine disruption, radiation-induced malignancies, cerebrovascular disease and headaches may also occur.

Spine complications of radiation therapy may include early or delayed myelopathy. Early brachioplexopathies are thought to be due to demyelination. The patient experiences pain and sensory changes as well as weakness of the arm. This can occur months after radiation therapy and typically is associated with a good prognosis. Late brachial plexopathies related to radiation typically occur greater than one year after completion of therapy. Typically the patient would experience weakness and sensory deficit without pain. The EMG can be associated with myokymia. Full recovery is rare.

As for chemotherapy, drugs are unable to easily penetrate the blood brain barrier. Some of the complications that can be associated with chemotherapy include aseptic meningitis, transverse myelopthy, encephalopathy, and peripheral neuropathy. For the majority of these complications, there is no specific treatment. Ultimately the drug must be reduced or discontinued and the symptoms are managed.

REFERENCE:

Neuro-oncology for the Masses CONTINUUM: Lifelong Learning in Neurology . 21(2, Neuro-oncology):299-300, April 2015.