High-grade Glioma

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The high grade gliomas are include the tumours following:

1. Glioblastomas (grade IV astrocytomas) (referred to as glioblastoma multiforme in older terminology)
2. Anaplastic astrocytomas (grade III astrocytomas)
3. Anaplastic oligodendrogliomas (grade III oligodendrogliomas)

These tumours usually grow rapidly and are not curable although various treatments can bring about a significant increase in survival time to many patients. Elderly and frail patients with these tumours are often referred to palliative care services quite soon after diagnosis where the plan is often best supportive care. Younger patients often receive numerous courses of surgery, radiotherapy and chemotherapy and are referred for palliative care services when their ability to mobilize and communicate starts to decline with progressive disease and complications of surgery. A decision faced by palliative care services often relates to site of care as the decline in function can be slow over weeks or months, and patients often end up in nursing homes for their final months of life.

Clinical features and complications

Patients usually present for the first time with symptoms and signs that have developed over a few days or weeks. Clinical features may include focal deficits from local destruction, headache and/or vomiting due to raised intracranial features or seizures.

Focal deficits

About 20% of patients have a focal deficit at presentation. The precise deficit of course relates to the location of the tumour, but some of the more common features are:

- Focal unilateral motor weakness
- Visual disturbances such as a homonymous hemianopia
- Speech disturbance such as a receptive dysphasia
- Memory loss
- Personality change

As the disease progresses focal neurological deficits are almost universal.

Headache

Around 60% of patients have headache due to raised intracranial pressure as a presenting symptom. The headache may be worse in the morning and be associated with morning vomiting.

Seizures

Around 55% of patients with grade III tumours present with seizures and about 25% of patients with grade IV tumours have seizures on presentation.

Rare symptoms and signs

Rarely high grade gliomas spread into the CSF causing features of leptomeningeal metastases such as back pain, cranial nerve palsies, confusion or headache.

Investigations

Imaging

A contrast-enhanced CT scan will usually show a large lesion however a gadolinium-enhanced MRI is the imaging investigation of choice. The following MR features are normally noted:

- T1-weighted images
  - Hypointense lesion
  - Surrounding hypointesnse oedema
  - Irregular contrast enhancement of lesion following contrast injection
- T2-weighted images
  - Increased signal intensity of lesion

Stereotactic biopsy

Although an MRI can be highly suspicious for a high grade glioma, a biopsy is required for definitive diagnosis. The biopsy can be done at the time of surgical resection, or if a patient is too unwell or frail for an operation, then a biopsy alone is usually appropriate. The biopsy itself is done by a neurosurgeon using stereotactic framing device. A sterotactical framing device is an external device that is attached to the patient's head and when used in conjunction with CT images, it can be used as a reference point to ensure that the correct area of the brain is being biopsied.

Treatment

The first-line treatment of high grade gliomas is surgical resection followed by adjuvant radiotherapy and chemotherapy.

Surgical resection

The principle of surgery is to maximally resect the glioma whilst preserving neurological function, which can sometimes be a difficult balance to get right. Intra-operative MRI can be used to evaluate if the resection has been complete, and if incomplete resection is noted, then further surgery can be

performed immediately, although there is no evidence currently that using intra-operative MR improves survival.

Histologically the tumours have poorly defined tumour margins and thus unfortunately local recurrence of tumour is very frequent even in patients with apparent complete removal of the tumour. Currently there is contradictory evidence regarding whether more extensive surgical resection improves length of survival.

Adjuvant chemotherapy and radiotherapy

Radiotherapy

Following surgery, radiotherapy (e.g. 60 Gray total over a 30 day course of fractions) has been shown to improve local control and survival and is standard treatment.

Chemotherapy

Adjuvant temozolamide when given in addition to radiotherapy improves progression-free and overall survival. It is an oral chemotherapy agent that is given concurrently with radiotherapy and then continued for 6 cycles (e.g. daily for 5 days every 4 weeks). In one study treatment with temozolamide improved overall survival from 11% at 1-year to 27% when compared with radiotherapy alone. The presence of MGMT positive biopsy is a key predictor of benefit from chemotherapy. In the same study, patients with MGMT positive tumours had a 15% 2-year survival compared to a 2% survival for patients with MGMT negative tumours.

Adverse effects of temozolamide include pancytopaenia. Thrombocytopaenia is very common and temozolomide is typically held if platelets < 100. In addition to neutropaenic sepsis patients are also at greater risk of Pneumocytis pneumonia, especially if they are also receiving concurrent steroids and patients are routinely given prophylaxis for this if they are lymphopaenic. Other side effects include nausea, vomiting and fatigue. 5-HT3 antagonists are given for nausea prevention and treatment. Rarely liver toxicity occcurs and LFTs should be monitored during treatment. Patients often receive 6 cycles. Some oncologists treat for 12 cycles.

Corticosteroids

Corticosteroids reduce tumour-associated oedema and often improve symptoms. Patients being treated with radiotherapy and chemotherapy (especially elderly patients) often have neurological deterioration (e.g. confusion) immediately following radiotherapy and these symptoms are often reversed with steroids. An initial dose of 8mg either once or twice daily dexamethasone is usual with a gradual dose reduction in the following weeks.

Prognosis at diagnosis

High grade gliomas are palliative illnesses with survival usually measured in months (for grade IV glioblastomas) to a few years (for grade III gliomas). The most important factors in predicting life expectancy are:

- Age (younger patients live longer)
- Tumour grade (anaplastic glioma patients live longer than glioblastoma patients)
- Karnofsky performance score (a lower score is associated with a shorter survival time)

- Tumour location
- Presence of MGMT positive biopsy (MGMT positive patients respond better to temozolamide)

A 2004 study grouped patients into one of four groups that helped define life expectancy:[1)]

Group 1	Age < 40 with a frontal tumour	Median survival of 132 weeks
Group 2	Age < 40 with a non-frontal tumour	Median survival of 71 weeks
Group 3	Age between 40-65 with a KPS >= 80 plus treated with surgical resection	Median survival of 63 weeks
Group 4	Age between 40-65 with a KPS >= 80 but no surgical resection (biopsy only)	Median survival of 44 weeks
	Age between 40-65 with a KPS ⇐ 0	Median survival of 38 weeks
	Age > 65	Median survival of 37 weeks

A study examining patients older than 70 with glioblastoma confirmed that a good KPS and resection are the most important factors in improving survival.

Group 1	Resection + aged between 70 and 75	8.5 month median survival
Group 2	Resection + age > 75	7.7 month median survival
Group 3	Age > 70, KPS >= 70, biopsy only	4.3 month median survival
Group 4	Age > 70, KPS < 70, biopsy only	3.1 month median survival

Recurrent disease and complications

Almost all patients develop recurrent disease within 5 years of initial therapy. Many patients have recurrence within months. For recurrent disease, treatments include further surgery, re-irradation and bevacizumab monoclonal antibody therapy.

Good palliative care is usually the key medical treatment with progression of disease. Corticosteroids can be used to reduce general symptoms such as headache or focal symptoms such as weakness and anti-convulsants are sometimes needed for seizures.

As ability to perform activities of daily living worsen increasing supports in the home setting are important and often the final weeks of care need to occur in a nursing home or hospice setting.

Seizures

Focal seizures (with or without secondary generalization) are a relatively common complications of high grade gliomas, although seizure incidence is less common in high grade gliomas compared to low grade gliomas with seizure rates of 50% in glioblastomas, 70% in anaplastic gliomas and 85% in low grade gliomas.

The type of seizure usually reflects the location of the tumour; sometimes there is secondary generalization. Occasionally status epilepticus can develop and in cases where this is non-convulsive status epielpeticus, the person presents with altered personality or a decreased conscious state and this can be quite difficult to diagnose (an EEG is required)

After a seizure has occurred initial treatment with mono-therapy is standard although there are no good trials that show which agent is best. Newer agents are geneally chosen as they tend to have less

adverse effects and less drug-drug interactions than the older agents. Levetiracetam is often the first choice agent chosen and has been shown to be as effective as older valproate, although several studies have suggested valproate may enahnce the anti-tumour effect of temozolomide. If a patient has further seizures after initiation of therapy the dose of the anti-convulsant should be increased. If inadequate seizure control occurs then a second agent should be added - valproate + levetiracetam is recommended.

Near the end of life, seizures become more common. About 40% of patients with a glioma have at least 1 seizure in their last month of life. Most of these are focal although about 1 in 5 of these patients have a generalied seizure; a very small proportion of these seizures develop into status epilepticus. In patients who cannot swallow and are on anti-convulsants near the end of their life, levetericateam can be given via continuous subuctaneous infusion. Sometimes a CSCI of midazoalm is appropriate (e.g. at a starting dose of 20mg over 24 hours). Stat doses of sublingual lorazepam or subcutaneous midazolam can be given PRN.

Seizure prophylaxis

Seizure prophylaxis is usually not recommended as there has been no good evidence to suggest a benefit with this, although post-operative prophylaxis (usually with phenytoin, and occasionally with levetiracetam) is often given for up to three months post-surgery.

Headache and raised intracranial pressure

Drowsiness and/or headaches from raised intracranial pressure are common as high grade gliomas progress. Sometimes it will be appropriate to treat this with corticosteroids whereas at other times analgesia and other supportive measures alone are more appropriate.

Corticosteroids reduce intracranial presure within hours of the first dose by decreasing capillary permability. The full effect takes several days. Dexamethasone is the usual agent because it has very little mineralocorticoid activity and so is unlikely to cause fluid retention. A common higher dose of dexamethasone for severe symptoms is 8mg twice daily; dexamethasone has a long half life and so once daily dosing is probably also reasonable. If the oral route is unavailable (e.g. in a patient with oropharyngeal dysphagia) then it can be subcutaneously.

As symptoms of raised intracranial pressure improve the dose can be gradaully reduced; for patients already on a small dose of dexamethasone, the dose can be gradually titrated up if there are worsening symptoms of raised intracranial presure. Concurrent use of a proton pump inhibitor is appropriate to reduce the risk of gastritis. Long-term problems with dexamethasone such as a proximal myopathy need to be weight into any thinking about dose and duration of treatment with steroids.

condition, oncology, neurosurgery, neurology, brain, textbook

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[1)] Lamborn, KR, Chang, SM, Prados, MD. Prognostic factors for survival of patients with glioblastoma: Recursive partitioning analysis. Neuro-oncology 2004