Protocol for Planning and Treatment

The process to be followed when a course of chemotherapy is required to treat:

Primary Anaplastic Oligodendroglioma and Anaplastic Astrocytoma Glioma Grade III

Patient information given at each stage following agreed information pathway

1. DIAGNOSIS

These rare tumours may present with a variety of neurological symptoms and signs, depending on anatomical location. They may develop on a background of a pre-existing low grade tumour.

After imaging suggestive of tumour, Tayside neurosurgeons will perform biopsy / debulking surgery and refer tissue samples to Edinburgh for review, where an expert neuropathology diagnosis is provided by Professor Ironside, Dr C Smith and Dr A Torgersen.

Definitive diagnosis of a Grade III anaplastic oligodendrolglioma or anaplastic astrocytoma is therefore based on the results of biopsy, or occasionally a radiological diagnosis of high grade glioma without tissue is accepted.

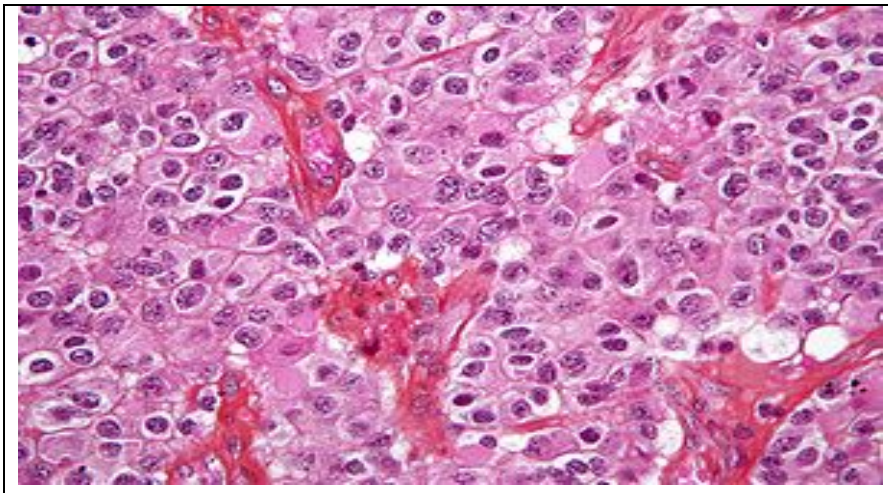
2. STAGING

Since these are localised tumours the staging investigations are based upon T1, T2 and T-gadolinium-enhanced MRI scan of the brain.

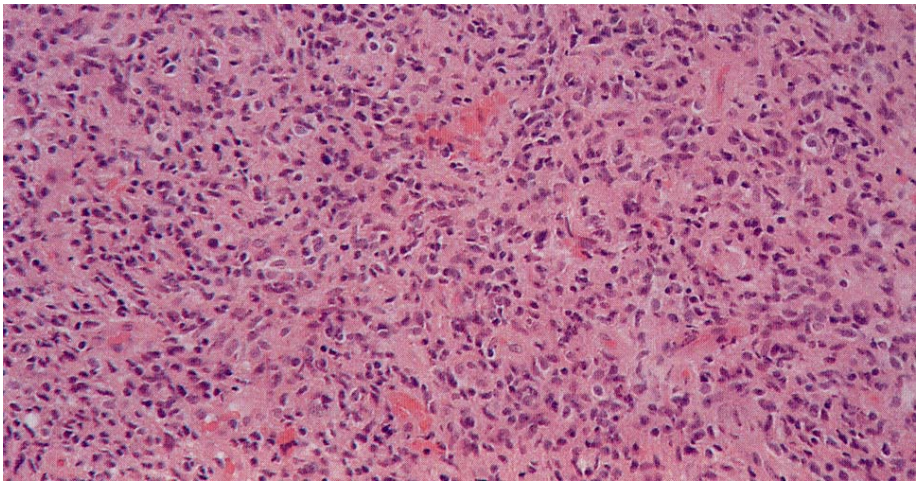
3. HISTOPATHOLOGY

Oligodendrogliomas are distinctive, consisting of homogeneous, compact, rounded cells with distinct borders and clear cytoplasm surrounding a dense central nucleus, giving them a "fried egg" appearance. There may also be areas of calcification. Classically they tend to have a vasculature of finely branching capillaries that may take on a “chicken wire” appearance.

They are associated with co deletion of chromosomal arms, 1p 19q (loss of heterozygosity: LOH) which has been found to predict for better outcomes and improved response to both chemotherapy and radiotherapy [1-4]. As such this should be assessed for, and treatment discussed in light of this result.



Anaplastic astrocytomas show increased anaplasia, with nuclear complexity, the presence of mitoses, cytoplasmic variability, and endothelial cell proliferation.



4. RADIOTHERAPY / SURGERY

Surgery

Where possible maximal surgical excision will be performed or appropriate safe debulking. In eloquent areas of the brain, a biopsy only may be appropriate.

Radiotherapy

Historically, first line treatment for anaplastic astrocytoma and anaplastic oligodendroglioma.

60Gy in 30# over 6 weeks or 54Gy in 30# over 6 weeks – see XRT protocol.

N.B.

A role for chemotherapy is developing – please see below**.**

5. CHEMOTHERAPY

Ip19 q status is of importance.

In co-deleted patients:

If the patient has 1p19q LOH, chemotherapy may be delivered post XRT.

EORTC 26951[(5)] randomised patients to 59.5Gy in 33# alone or followed by 6 cycles of standard dose PCV.

In co-deleted patients, the addition of chemotherapy showed a marked improvement in PFS (157 vs. 50 months HR 0.42 CI 0.24 – 0.74) and an as yet not fully quantified improvement in OS (not yet reached vs. 112 months).

In the overall population, a 12 month improvement in median OS (42 vs 30 months) was seen.

In non co-deleted patients:

In the same study, there is a trend towards improved OS, but no significant difference in non deleted patients. PFS was improved from 15 to 9 months (HR 0.73 CI 0.56 – 0.97). As such, the role of PCV is less clear cut, but can be discussed with individual patients.

NOTE: PCV in toxic to marrow. Whilst no trials have yet reported the role of Temozolomide in this setting, this may be a reasonable alternative, given for 6 – 12 months post XRT. Prospective phase III data are still awaited to establish role of TMZ (CATNON study)

In frail patients, or those with large XRT fields, and who have an oligodendroglial component and are co-deleted:

It may reasonable to use chemotherapy as sole first line treatment, sparing the toxicity of XRT. The ongoing CODEL study may answer this question. NOA -4 [6] showed no difference between either modality first line

Relapse:

PCV or TMZ may be used at relapse, in either tumour subtype irrespective of 1p19q status.

Definitions:

PCV

Lomustine 100 mg/m² po Day 1
Procarbazine 100 mg/m² po Days 1 -10
Vincristine 1.5 mg/m² iv Day 1 (Max 2mg)

Repeated every 6 weeks for a maximum of 6 cycles.

Temozolomide

Temozolomide 200mg/m^2 oral d1-5 q28 days for 6 (up to 12 cycles at relapse).

6. SUPPORTIVE THERAPY

All patients with brain tumours should be referred to a specialist nurse. Patients may wish to have support from the Macmillan Nurse in the community and they should be told of the opportunity of visiting the Macmillan Centres at Roxburghe House, Macmillan House, Perth or Macmillan Centre at Stracathro and Maggie's Centre in Dundee.

Dexamethasone to reduce cerebral oedema is often needed by these patients, but the minimum dose required to control symptoms should be used. Gastric protection in the form of a proton pump inhibitor should be prescribed. All patients should carry a steroid card at all times.

7. TREATMENT DEFINITIONS

PCV

Lomustine 100 mg/m² po Day 1
Procarbazine 100 mg/m² po Days 1 -10
Vincristine 1.5 mg/m² iv Day 1 (Max 2mg)

Temozolomide

Temozolomide 150 - 200mg/m^2 oral d1-5 q28 days for 6 cycles

8. REVIEW

Patients treated with XRT

Weekly review through XRT by radiotherapy support team.

To be seen in clinic 4 weeks after completion of XRT to assess toxicities and to discuss adjuvant chemotherapy. If not proceeding to chemotherapy, MRI / CT at 2-3 months to assess response to treatment.

Patients treated with chemotherapy

For patients receiving adjuvant chemotherapy, to be reviewed in clinic with baseline imaging post XRT, and after cycle 3 and 6, to assess toxicities and with MRI / CT to assess response to treatment.

9. REFERENCES

1. C. Walker et al "Clinical use of genotype to predict chemosensitivity in oligodendroglial tumors" Neurology 2006;66:166 http://www.neurology.org/cgi/content/abstract/66/11/1661

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4. Labussiere M et al "*IDH1* Gene Mutations: A New Paradigm in Glioma Prognosis and Therapy? The Oncologist February 2010 vol. 15 no. 2 196-199
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6. Wick W et al NOA-04 Randomized Phase III Trial of Sequential Radiochemotherapy of Anaplastic Glioma With Procarbazine, Lomustine, and Vincristine or Temozolomide JCO VOL27 35 DE10 2009 http://jco.ascopubs.org/content/27/35/5874.full.pdf