Clinical Commissioning Policy: Temozolomide as adjuvant treatment for people with newly diagnosed anaplastic astrocytoma without 1p/19q codeletion following surgery and radiotherapy (Adults)

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Clinical Commissioning Policy: Temozolomide as adjuvant treatment for people with newly diagnosed anaplastic astrocytoma without 1p/19q codeletion following surgery and radiotherapy (Adults)

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Policy Statement

NHS England will commission temozolomide as adjuvant treatment for people with newly diagnosed anaplastic astrocytoma without 1p/19q codeletion following surgery and radiotherapy (Adults) in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About anaplastic astrocytoma

Astrocytomas are a form of brain cancer. They grow from a type of cell in the brain called an astrocyte, which is the most abundant cell in the brain and is responsible for protecting nerve cells in the central nervous system. There are various types of astrocytomas which can affect both adults and children. About one third of all brain cancers in the UK are astrocytomas (The Brain Tumour Charity, 2015).

Astrocytomas are classified based on how fast they grow and how likely they are to spread using a grading system. Grade 3 astrocytomas are referred to anaplastic astrocytomas and are fast growing cancers which often re-occur after initial treatment (The Brain Tumour Charity, 2015). The condition is more common in adults between the ages of 30 and 70 years and in males. Overall, about 27% of people diagnosed with anaplastic astrocytoma live for five years or more (The Brain Tumour Charity, 2015).

About current treatments

Because anaplastic astrocytomas are fast growing, surgery is usually the primary treatment option. The aim of surgery is to remove all or as much of the tumour as possible. This is usually followed by adjuvant treatment involving radiotherapy, to reduce the risk of the cancer coming back. Some people may also have chemotherapy after surgery.

About the new treatment

Temozolomide is an oral medicine that works by stopping cancer cells from making deoxyribonucleic acid (DNA), thereby preventing cell growth. It is proposed to be an additional adjuvant treatment option for people with newly-diagnosed anaplastic

astrocytoma who have already been treated with surgery and radiotherapy and who do not have a 1p/19q codeletion genetic marker, as this is associated with a poor chemotherapy response rate and worse prognosis. Temozolomide is not licensed for use in this indication.

What we have decided

NHS England has carefully reviewed the evidence to newly-diagnosed anaplastic astrocytoma without evidence of 1p/19q codeletion with adjuvant temozolomide (following surgery and radiotherapy) and has concluded that the treatment should be routinely commissioned.

1 Introduction

Clinical indication

Astrocytomas are a type of brain tumour that develop from cells called astrocytes. Astrocytes are star-shaped cells responsible for protecting the nerve cells in the central nervous system.

Astrocytomas are classified by the World Health Organisation (WHO) grading system based on how fast the cells grow and the likelihood of them spreading to nearby tissue. Grade 1 and 2 astrocytomas are 'low-grade' tumours, meaning they are slow-growing and unlikely to spread to other parts of the brain. Grade 3 and 4 astrocytomas are 'high-grade' tumours, meaning they are fast growing and more likely to recur and / or spread to other parts of the brain.

Grade 3 astrocytomas are referred to as anaplastic astrocytomas. The standard treatment for people with newly diagnosed anaplastic astrocytomas is surgery followed by adjuvant radiotherapy. Some people may also have chemotherapy.

Response to treatment can be dependent on genetic markers. People without 1p/19q co-deletion do not respond as well to chemotherapy and have a worse prognosis than those with the codeletion (van den Bent et al. 2006). This policy is specifically for people with anaplastic astrocytomas without 1p/19q co-deletion.

Proposed intervention

Temozolomide is a chemotherapy treatment that works by stopping cancer cells from making DNA. Temozolomide is taken orally and is unlicensed for the treatment of newly-diagnosed anaplastic astrocytoma. It is proposed that temozolomide be administered following surgery and usually within four weeks of completing radiotherapy for people with newly-diagnosed anaplastic astrocytoma without 1p/19q codeletion. It should be given for up to 12 cycles with each cycle lasting four weeks and administered at 150-200 mg/m2 on days 1 to 5 of each cycle.

Use of temozolomide in the treatment of newly-diagnosed anaplastic astrocytoma is supported by the National Institute for Health and Care Excellence (NICE) clinical guideline on brain tumours (primary) and brain metastases in adults (NICE, 2018, Reference: NG99).

2 Definitions

1p/19q codeletion – A genetic mutation which involves the deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q).

Adjuvant treatment - Additional cancer treatment given after the primary treatment to lower the risk of the cancer coming back.

Anaplastic astrocytoma - A type of brain tumour, developing from astrocytes.

Astrocyte - Star-shaped cells that surround and protect nerve cells in the central nervous system.

Biomarker – A naturally occurring characteristic which can indicate responses to treatment.

Chromosome – One of the structures of a cell which carry genetic information.

World Health Organisation (WHO) Performance status - An international scoring system used to quantify a cancer patient's general well-being and activities of daily life. The measure is used to assess how well a person may tolerate treatment such as chemotherapy.

Malignant - A term for diseases in which abnormal cells divide without control and can invade nearby tissues.

Overall survival (OS) – The length of time from either diagnosis or start of treatment that the patient is still alive.

Progression free survival (PFS) – The length of time from start of treatment to when the disease gets worse or death.

3 Aims and Objectives

This policy considered: Temozolomide as adjuvant treatment for people with newly-diagnosed anaplastic astrocytoma without 1p/19q codeletion following surgery and then radiotherapy.

The objectives were to establish, via an evidence review, the following:

- The clinical effectiveness, safety and cost-effectiveness of 12 months of adjuvant temozolomide following surgery and radiotherapy compared to surgery and radiotherapy alone

4 Epidemiology and Needs Assessment

There are around 11,500 new brain, other central nervous system and intracranial tumours cases in the UK every year. Astrocytomas account for one third of all brain cancer diagnoses in the UK. Incidence rates for brain tumours are projected to rise by 6% in the UK between 2014 and 2035, to 22 cases per 100,000 people by 2035 (Cancer Research UK).

A recent Australian publication indicates an incidence of anaplastic astrocytoma was an age-adjusted rate of 3.5 per million person/years (Smoll and Hamilton, 2014). The Policy Working Group estimate that the annual incidence of newly-diagnosed anaplastic astrocytoma in adults would be between 185 – 200 cases per year in England.

5 Evidence Base

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of Temozolomide as an adjuvant treatment for people

with newly diagnosed anaplastic astrocytoma without 1p/19q codeletion following surgery and radiotherapy.

Clinical Effectiveness

Overall survival

The interim results from an ongoing open-label randomised controlled trail (RCT) reported by van den Bent et al. (2017) involving 745 adults with anaplastic glioma without 1p/19q codeletion, found that people treated with up to 12 cycles of adjuvant temozolomide (following surgery and radiotherapy; treatment cycle consists of 5 treatment days followed by a 23 day treatment interruption) had significantly better overall survival compared with people not treated with adjuvant temozolomide (primary efficacy outcome).

The hazard ratio (HR) for overall survival for adjuvant temozolomide was 0.65 (99.145% confidence interval [CI] 0.45 to 0.93, p=0.0014).

Overall survival at 5 years was 55.9% (95% CI 47.2 to 63.8) for people treated with adjuvant temozolomide, compared with 44.1% (95% CI 36.3 to 51.6) for people not treated with adjuvant temozolomide.

Median overall survival could not be calculated because the minimum number of deaths had not occurred in the adjuvant temozolomide groups at the time of the interim analysis.

Sub-group analysis of overall survival

The investigators assessed overall survival in people treated with 12 cycles of adjuvant temozolomide, adjusted for the following baseline characteristics: age, WHO performance status, 1p loss of heterozygosity, presence of oligodendroglial elements and MGMT [O6-methylguanine-DNA methyltransferase] promotor methylation before randomisation.

The investigators found that people aged over 50 years had significantly worse overall survival compared with people aged 50 years and under (HR 4.04, 99.145% CI 2.78 to 5.87, p<0.0001). People found to have MGMT-promotor methylation before randomisation had significantly better overall survival compared with people

without MGMT-promotor methylation (HR 0.49, 99.145% CI 0.26 to 0.93, p=0.0031). WHO performance score, 1p loss of heterozygosity and presence of oligodendroglial elements did not significantly affect overall survival in people treated with adjuvant temozolomide (all p>0.01).

It should be noted that such sub-group analyses of interim trial results are likely to be underpowered and should be interpreted with caution. The final results of the study are needed to determine which subgroups of people may benefit most from treatment with adjuvant temozolomide.

Progression-free survival

The RCT by van den Bent et al. (2017) found that people treated with adjuvant temozolomide had significantly better progression-free survival compared with people not treated with adjuvant temozolomide (secondary efficacy outcome). Median progression-free survival was 42.8 months (95% CI 28.6 to 60.6) for people treated with adjuvant temozolomide, compared with 19.0 months (95% CI 14.4 to 24.6) for people not treated with adjuvant temozolomide.

Progression-free survival at 5 years was 43.1% (95% CI 35.0 to 50.9) in people treated with adjuvant temozolomide, compared with 24.3% (95% CI 17.7 to 31.6) in people not treated with adjuvant temozolomide.

Safety and tolerability

The interim results from an ongoing open-label RCT (van den Bent et al. 2017) reported that over a median 27-month follow-up, 8–12% of people treated with temozolomide (n=549; including people on concurrent therapy) had grade 3–4 toxicity. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Grade 3 toxicity refers to severe adverse events and grade 4 refers to life-threatening or disabling adverse events.

The majority of grade 3–4 toxicities were haematological in nature, with the most frequent events in the adjuvant temozolomide group (n=182) being thrombocytopenia (9.3%), neutropenia (4.4%), leukopenia (2.2%) and anaemia

(1.1%). The most frequently reported non-haematological grade 3–4 toxicities in people treated with adjuvant temozolomide were infections (7.9%), constitutional symptoms (which were not defined in the paper, but normally include fever, weight-loss and fatigue; 6.8%) and gastrointestinal events (5.6%).

Grade 3–4 increases in aminotransferase concentration, an indicator of possible liver damage, occurred in 5 participants (1%) receiving temozolomide. In 2013, the MHRA issued a safety warning on the risk of hepatic injury, including fatal hepatic failure, with temozolomide.

In total, 30 people (8%) discontinued treatment with adjuvant temozolomide because of toxicity, although further details are not reported.
Across the 2 adjuvant temozolomide groups, 262 participants completed or stopped taking temozolomide before the interim analysis. Of these, 167 participants (64%) had at least 1 cycle of temozolomide delayed. The reasons for a delay were haematological adverse events (28%), non-haematological adverse events (6%), both haematological and non-haematological adverse events (3%) and reasons not related to treatment (47%).

The Summary of Product Characteristics (SPC) for temozolomide reports the frequency of adverse events from clinical trials involving people with newly-diagnosed glioblastoma and recurrent or progressive malignant glioma. Very common (reported by 1 in 10 people or more) adverse events include:

- anorexia
- headache
- constipation, nausea and vomiting
- rash
- alopecia
- fatigue
- neutropenia, lymphopenia or thrombocytopenia.

Cost-effectiveness

No studies were identified during literature searches (see search strategy for full details) that compared the cost-effectiveness of adjuvant temozolomide in people with newly-diagnosed grade 3 anaplastic astrocytoma without evidence of 1p/19q codeletion. The study included in this evidence review did not include an outcome investigating cost-effectiveness.

6 Criteria for Commissioning

Inclusion criteria

People will be eligible for treatment under this policy who:

- Have newly-diagnosed, grade 3 anaplastic astrocytoma;
- Have no 1p/19q co-deletion (confirmed by pathological testing);
- Have been previously treated with surgery and radiotherapy;
- Are over 18 years of age; and
- Have a WHO performance status 0-2.

Exclusion criteria

People excluded for treatment under this policy will:

- Have 1p/19q co-deletion (confirmed by pathological testing); and/or
- Have a WHO performance status of 3-4.

Starting criteria

The decision to treat with temozolomide must be made by the neuro-oncology multi-disciplinary team (MDT), hosted by a neurosurgical centre, and the patient. The first cycle must be prescribed by a neuro-oncologist who is core member of the neuro-oncology MDT and is specifically trained and accredited in the use of systemic anti-cancer therapy.

Adjuvant treatment with temozolomide should begin within four weeks of completing radiotherapy treatment. Where this is not possible due to other clinical factors (e.g.,

due to wound infection), temozolomide must administered within three months of completing radiotherapy treatment (van den Bent et al., 2017).

Stopping criteria

Magnetic resonance imaging (MRI) scans should be performed every 3 months, with treatment stopping if progressive disease occurs.

7 Patient Pathway

The patient pathway in accessing this treatment will be through a neuro-oncology MDT. This reflects existing care pathway arrangements for patients with brain and CNS cancers.

8 Governance Arrangements

As temozolomide is not a licensed medicine for this indication, any provider organisation treating patients with this intervention will be required to provide assurance that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Providers will be expected to follow Trust and Cancer Alliance policies for the safe prescribing and monitoring of off-label licensed medications including compliance with MHRA safety alerts. Prescribers need to also be aware of their responsibilities as specified in MHRA Drug Safety Update volume 10 issue, 12 July 2017:2.

9 Mechanism for Funding

Temozolomide will be funded by local specialised commissioning teams, through established chemotherapy funding arrangements

10 Audit Requirements

Systemic Anti-Cancer Treatment (SACT) dataset.

11 Documents which have informed this Policy

- NHS England, 2018. Evidence Review: Policy 1691.
- NICE, 2007. NICE Technology Appraisal: Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (TA121).
- NICE, 2016. NICE Technology Appraisal: Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (TA23)
- NICE, 2018. NICE Guideline: Brain tumours (primary) and brain metastases in adults (Guideline NG99).

12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

13 References

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Smoll NR and Hamilton B. (2014). Incidence and relative survival of anaplastic astrocytomas. Neuro-oncology 16(10): pp1400-7. Doi:10.1093/neuonc/nou053. Available at: - https://www.ncbi.nlm.nih.gov/pubmed/24723565 [Accessed 1st March 2019]

Van den Bent MJ, Baumert B, Erridge B et al. (2017) Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. Lancet 390:1645–53

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