Summary: Brain Tumour Related Epilepsy (BTRE) has a significant impact on Quality of Life with implications for driving, employment, and social activities. Management of BTRE is complex due to the higher incidence of drug resistance and the potential for interaction between anti-cancer therapy and anti-seizure medications (ASMs). Neurologists, neurosurgeons, oncologists, palliative care physicians and clinical nurse specialists treating these patients would benefit from up-to-date clinical guidelines. We aim to review the current literature and to outline specific recommendations for the optimal treatment of BTRE, encompassing both Primary Brain Tumours (PBT) and Brain Metastases (BM). A comprehensive search of the literature since 2000 on BTRE was carried out in PubMed, MEDLINE and EMCARE. A broad search strategy was used, and the evidence evaluated and graded based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence.

Seizure frequency varies between 10-40% in patients with Brain Metastases (BM) and from 30% (high-grade gliomas) to 90% (low-grade gliomas) in patients with PBT. In patients with BM, risk factors include number of BM and melanoma histology. In patients with PBT, BTRE is more common in patients with lower grade histology, frontal and temporal tumours, presence of an IDH mutation and cortical infiltration.

All patients with BTRE should be treated with ASMs. Non-enzyme inducing ASMs are recommended as first line treatment for BTRE, but up to 50% of patients with BTRE due to PBT remain resistant. There is no proven benefit for the use of prophylactic ASMs, although there are no randomised trials testing newer agents. Surgical and oncological treatments i.e. radiotherapy and chemotherapy improve BTRE. Vagus Nerve Stimulation has been used with partial success.

The review highlights the relative dearth of high-quality evidence for the management of BTRE and provides a framework for further studies aiming to improve seizure control, quality of life, and indications for ASMs.

Keywords: seizures, anti-seizure medications, anti-convulsants, primary brain tumours, brain metastases

Key Points:

- Offer levetiracetam or lamotrigine to all patients with primary or metastatic brain tumours who have seizure(s).
- ASM withdrawal for patients in remission is not recommended due to high rates of seizure recurrence.
- ASM prophylaxis is not generally recommended in the management of seizure-naïve patients.
- ASM for BTRE is safe in pregnancy and breastfeeding

Introduction

Epileptic seizures are among the most common presenting symptoms in patients with an underlying brain tumour. Brain Tumour Related Epilepsy (BTRE) occurs as a presenting symptom in 30-90% of patients with primary brain tumours,[1] and 15-40% of patients with brain metastases (BM).[2] A further 10-30% of brain tumour patients will develop seizures at some point during their disease course.[1,2] BM are the most common type of brain tumour in adults and are increasing in frequency due to improved systemic treatments prolonging the survival of patients with extracranial primary brain tumours.[3] Seizures in brain tumour patients contribute to significant comorbidity and substantially impact Quality of Life. They add an additional psychosocial burden, negatively affecting the independence of patients which includes the withdrawal of their driving license.[4] Management of BTRE is inherently more complex due to the higher incidence of drug resistance and the additional need for oncological treatment which may interact with anti-seizure medications (ASMs).

There is a paucity of clinical guidelines for the management of BTRE. In this paper we review the latest evidence around modern ASMs and oncological treatments for both primary

and metastatic BTRE, and outline recommendations for optimal management based on this evidence.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[5]. The final study protocol was registered with the PROSPERO international prospective register of systematic reviews (https://www.crd.york.ac.uk/PROSPERO/, registration number CRD42021261505). Inclusion criteria were studies reporting primary or secondary brain tumours, and the management of epilepsy in these patients. Case-control, cohort and population-based studies, and randomised control trials were included. All studies were required to have ethical approval to share the data. Animal studies, editorials, letters, conference abstracts and non-peer reviewed publications were excluded. Studies including less than 10 patients, published in any language other than English, published before 1995 or not describing outcomes of management of BTRE were also excluded. The study search and selection were done by two independent reviewers.

Search strategy

The search strategy was designed in consultation with a medical librarian with expertise in systematic reviews. In this systematic review we searched PubMed, Medline and EMCARE databases for articles published from January 1 1995 to June 28 2021 (Appendix 1) using terms relating to brain tumours and epilepsy. In addition, we hand-searched the bibliographies of included articles for further relevant articles. The most recent electronic search was completed on 28 June 2021.

Study selection

Two reviewers independently screened the abstracts of papers that were yielded from the search. Following this, full texts were accessed and examined against the inclusion and exclusion criteria. Each study was graded based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence. This was followed by a descriptive analysis of the main outcomes.

Results

1563 abstracts and titles were identified through our electronic search. Of the titles screened, the full texts of 129 articles were reviewed for eligibility (Figure 1). Three additional abstracts were identified by manually searching the bibliographies of included articles. 64 articles were included in our systematic review. The quality of evidence was in general judged to be Level 2 and below (Figure 2).

Discussion

Risk factors

Risk factors for BTRE in patients with primary brain tumours include tumour grade, location and histology. There is a well-established paradox whereby slow-growing, low-grade brain tumours are associated with a higher risk of seizures than more aggressive high-grade tumours.[1,6] Cortical tumours are more epileptogenic than subcortical or infratentorial tumours.[1] Furthermore, tumours in the frontal, temporal or parietal lobes are more commonly associated with seizures than tumours in the occipital lobe.[7] Oligodendrogliomas, which are

more often located in the cortex, are more prone to causing seizures than astrocytomas.[8] The presence of an IDH 1 mutation is a significant factor increasing the risk of seizures.[9, 10]

Risk factors associated with metastatic BTRE are primary tumour type, number, site (supratentorial and frontal location) and volume of metastases. Seizure rates are higher in patients with melanoma and ovarian metastases compared to lung and breast metastases, in patients living in an urban environment and those of African American race.[2, 11-14]

General Principles of BTRE Management

Optimal management of BTRE involves achieving tumour and seizure control, thereby improving quality of life and prolonging survival. The goals of BTRE management are to reduce the frequency of seizures (ideally to seizure freedom) with an acceptable safety profile and tolerability of ASMs, without interfering with the efficacy of anti-tumour treatment.[15] This requires an integrated approach between neurologists, neurosurgeons and oncologists.

ASMs are the mainstay of treatment to achieve seizure control in BTRE.[16] In addition, seizure control is improved by the successful treatment of the underlying brain tumour. Surgery, radiotherapy, and chemotherapy have all been shown to be effective in improving seizure control in patients with brain tumours.[17]

Anti-Seizure Medications (ASMs)

ASMs should be started as soon as possible after a seizure in a patient found to have a brain tumour or already diagnosed, as the risk of seizure recurrence is high. Cytochrome p450

enzyme-inducing anti-seizure medications (EIASMs) e.g. carbamazepine and phenytoin, should be avoided, as these drugs compromise chemotherapeutic agent efficacy and have multiple drug interactions e.g. hormonal contraception, corticosteroids.[17] Previously EIASMs were the only drugs available but newer ASMs, such as levetiracetam and lamotrigine, are now used as first-line therapy.[18-20]

The use of lamotrigine as a first-line ASM for partial seizures is supported by the SANAD trial which found lamotrigine to be superior to carbamazepine, gabapentin, topiramate and oxcarbazepine in terms of time to treatment failure, although patients with brain tumours were specifically excluded from this study.[21]

The evidence for the optimal ASM monotherapy for BTRE has been presented in a recent systematic review of 66 studies, which concluded that levetiracetam, phenytoin and pregabalin seemed to be the most effective ASM monotherapy for patients with gliomas and epilepsy. Levetiracetam showed the lowest treatment failure rate with an efficacy (as measured by $\geq$ 50% reduction in seizure frequency) of 82% and 97% at 6 and 12 months respectively.[22] As phenytoin is an EIASM with a high rate of adverse events in brain tumour patients and pregabalin is only licensed as adjunctive therapy for patients with focal seizures, levetiracetam should be used first-line.

The LaLiMo Trial compared levetiracetam with lamotrigine in an open-label, prospective Randomised Controlled Trial. [23] This study included patients with both focal and generalised epilepsy with a primary endpoint of proportion of patients who were seizure-free after 6 weeks (67.5% in levetiracetam group, 64% in lamotrigine group). There were no major differences in efficacy or tolerability, but there was more rapid titration in the levetiracetam

group. It is difficult to draw any conclusions about long-term efficacy of these drugs from this study. Similarly, a retrospective study comparing treatment-failure of first-line monotherapy with either levetiracetam (776 patients) or valproate (659 patients) showed superior efficacy of levetiracetam (16% treatment failure due to uncontrolled seizures for levetiracetam compared to 28% for valproate) but no difference in adverse events (14% levetiracetam vs 15% valproate).[24]

An observational study of long-term retention of three ASMs, levetiracetam, lamotrigine and topiramate over 2 years suggested that more patients were likely to remain on lamotrigine than levetiracetam (69.2% vs 45.8%) but that seizure freedom rates were lower in patients on lamotrigine compared to levetiracetam.[25] Together with data from small trials specifically in BTRE that show an efficacy of levetiracetam in achieving seizure freedom between 76-91%, we support the consensus that levetiracetam is the preferred monotherapy in BTRE due to proven effectiveness, tolerability and lack of drug interactions.[26]

After levetiracetam and lamotrigine, lacosamide, topiramate, perampanel, sodium valproate brivaracetam and zonisamide can all be considered. Lacosamide[27,28] and perampanel [29] have shown to be effective and well tolerated as adjunct therapy in small studies. Lacosamide has been evaluated as an add-on in a prospective multicentre observational study and showed good efficacy (77% were 50% responders and 35% were seizure free) and tolerability (4.3% discontinuing due to adverse drug reactions.[28]

Prophylaxis with ASMs

The prophylactic use of ASMs in seizure-naïve brain tumour patients has been debated extensively.[30] There is no evidence to support the prescription of ASM in patients with brain tumours who have never experienced a seizure. In 2000, the American Academy of Neurology published guidelines discouraging the routine use of ASM prophylaxis in patients with newly diagnosed brain tumours.[31] These guidelines were based on four Randomised Controlled Trials and eight cohort studies, none of which demonstrated statistically significant improvements in the Odds Ratio for seizure-free survival or seizure incidence with ASM prophylaxis. One of the Randomised Controlled Trials in 1996 showed that sodium valproate prophylaxis in brain tumour patients had a nonsignificant increased rate of seizures compared to the placebo group.[32] A 2020 Cochrane Review of ten Randomised Controlled Trials which included 1815 seizure-naïve patients undergoing craniotomy found there was no evidence to suggest that ASM prophylaxis decreased the risk of seizures.[33] The most recent guidelines published by the Congress of Neurological Surgeons and endorsed by the American Society of Clinical oncology (ASCO) and Society for Neuro-Oncology (SNO) do not recommend the use of ASMs for patients with BM who do not undergo surgical resection and who are seizure free.[34]

Despite the lack of evidence for ASM prophylaxis, the practice is still widespread.[35] A Randomised Clinical Trial of 146 patients showed that levetiracetam was superior to phenytoin in preventing seizures in patients with supratentorial tumours peri-operatively and was better tolerated.[36] The incidence of seizures was 1.4% in the levetiracetam group and 15.1% in the phenytoin group ($p=0.005$). The increased efficacy and better side effect profile of levetiracetam makes it the most common drug used prophylactically, as measured by

surveys undertaken by the American Association of Neurological Surgeons (85% levetiracetam use) and the Korean Society for Neuro-Oncology (82.9% levetiracetam use).[37] Comparing the 2005 American Association of Neurological Surgeons survey to its 2017 edition, illustrates the shift away from phenytoin in 2005 (96% phenytoin use) to levetiracetam in 2017 (85% levetiracetam use). [38]

A Randomised Controlled Trial of 123 patients with Brain Tumours (77 brain metastases, 46 gliomas) undergoing surgery compared 7-day prophylaxis with phenytoin to no prophylaxis, but the trial was closed before completion. At the time of trial closure, there was no statistically significant difference in the incidence of early seizures (< 30 days after surgery) between the two groups.[39] Similarly, a retrospective study of 258 patients with BM reported ASM prophylaxis did not reduce the incidence of seizures.[40] However, a retrospective analysis of melanoma patients with supratentorial BM found that patients taking prophylactic ASM remained seizure free at 3 months.[41] Seizure risk in patients not receiving ASM at diagnosis was 20%.

The ongoing Seizure Prophylaxis IN Glioma (SPRING) trial will be crucial in providing clinicians with a well-designed RCT to inform clinical practice. Over 800 patients with suspected supratentorial glioma will be randomised to receive levetiracetam or placebo, prior to craniotomy, and will continue treatment up to a year post surgery. The primary endpoint will be one-year risk of first seizure, with secondary end points including time to first seizure, survival and quality of life measures.[42]

Withdrawal of ASMs

The presence of a symptomatic tumour is associated with an increased risk of seizure recurrence after ASM withdrawal. However, it is recognised that some patients with BTRE, particularly those with indolent gliomas who are seizure free after anti-tumour treatment may wish to discontinue ASMs. An observational study of 46 glioma patients who withdrew ASM treatment after being seizure-free for more than 1 year since their last anti-tumour treatment or more than 2 years since their last seizure, the rate of seizure recurrence was 26% after ASMs were withdrawn compared with 8% of patients who continued ASM treatment. [43]

A comprehensive literature review from 1990–2016 addressing ASM withdrawal in glioma patients reported that there was a paucity of evidence to support a policy of ASM withdrawal but that it could be considered in patients with stable gliomas associated with a favourable prognosis and long-term seizure freedom. The authors reflected that the potential benefits of ASM withdrawal need to be carefully weighed against the risk of seizure recurrence in a shared decision-making process, and carefully discussed particularly with those patients who depend on holding a driving licence.[44]

ASMs and survival

Initial reports suggested a possible survival advantage in glioblastoma (GBM) patients treated with valproic acid[45, 46] and more recently levetiracetam.[47, 48] However a survival analysis pooling over 1800 patients with GBM treated in four randomised clinical trials did not show any improvement in either Progression Free Survival or Overall Survival with either drug and so there is no justification to use these drugs except for seizure control.[49]

Effect of Oncological Treatments on Seizure Control

Surgery

Surgical resection is the mainstay of primary treatment for most primary brain tumours and has been shown to improve seizure control in gliomas. Chang et al. (2008) reported 67% of patients were seizure free one year after surgery in a retrospective analysis of 269 patients with low-grade gliomas and epilepsy. Gross-total resection was better than sub-total resection and was the best prognostic indicator for seizure freedom post-surgery.[8] A recent single center retrospective analysis of 128 consecutive patients operated for low-grade gliomas, all of whom had seizures, calculated a resection threshold of 80% to obtain seizure freedom, which is similar to that reported for an overall survival benefit. [50] A similar study found that an Extent of Resection of more than 91% and a postoperative tumour volume of less than 19 ml was necessary for optimal seizure control.[51]

There is growing evidence to support earlier resection of low-grade gliomas as opposed to watchful waiting both for improved seizure outcomes and survival. In a retrospective analysis of 153 adults comparing two similar cohorts of patients treated eleven years apart, the proportion of patients with intractable epilepsy reduced from 72.2% in 2006 to 43.2% in 2017 ($p<0.05$).[52] The only difference between the two cohorts was the rate of early surgery (21% in the 2006 cohort compared with 61% in the 2017 cohort) without an increase in neurosurgical morbidity.

Radiotherapy

Radiotherapy and chemotherapy both reduce seizure frequency.[53] The EORTC 22845 trial compared early postoperative radiotherapy with delayed radiotherapy and found early radiotherapy improved seizure control after 1 year.[54] In a retrospective analysis of 43 patients with low-grade (33) and high-grade (10) gliomas, seizure reduction was significant (≥50% reduction of frequency compared to baseline) in 72% of patients 3 months after radiotherapy.[55] Seizure freedom (Engel classification I) was achieved at 1 year in 32% of all patients and 38% of patients with grade II tumours.

It has been suggested that radiotherapy, whether whole brain, partial brain or Stereotactic Radiosurgery (SRS), may provoke seizure activity by increasing brain oedema (acute adverse event) or as a manifestation of radiation necrosis (late toxicity). A few limited retrospective studies have investigated the relationship between BM, its treatment, and the development of seizures but much of the literature also includes patients with primary brain tumours.

There are limited data for seizure activity assessment post SRS. In a review on outcomes post-SRS in 316 lesions treated in 273 patients, new neurological complications were seen in 101/316 (32%) lesions treated, but of these only 41/316 (13%) were new seizures.[56] In a separate retrospective study of 258 patients with lung cancer BMs, treated with gamma knife radiosurgery, 12.4% developed de novo seizure activity after treatment.[57]

There is clearly a need for prospective studies in the modern era of SRS that specifically address the incidence and risk factors for seizure development in patients with BM.

Chemotherapy

There are no Randomised Controlled Trials investigating seizure outcome after chemotherapy. 14 studies (7 prospective and 7 retrospective) report seizure outcome data after chemotherapy in gliomas. Four studies used Engel classification as the seizure outcome measure. In these studies, chemotherapy with procarbazine- lomustine-vincristine (PCV) or temozolomide was associated with improved seizure control in 30-100% of patients. [53] In the only study to include an observational control group, seizure frequency in patients with intractable epilepsy was analysed before and after treatment with the alkylating agent temozolomide. There was a reduction in seizure frequency of greater than 50% per month in 59% of patients receiving temozolomide compared to 13% of patients who did not receive temozolomide ($p < 0.001$).[58]

Non-Pharmacological Management of Intractable BTRE: Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) represents a possible approach as adjunctive therapy in BTRE patients who have intractable seizures and are not candidates for tumour resective surgery.

In a retrospective study of 16 patients with primary brain tumours who had VNS, 50% of patients had improvement in seizure frequency after an average follow up of 40 months.[59] Seizure frequency decreased by 10.9% in patients with progressing tumours and 65.6% in patients with stable tumours. In a larger case-control study of 107 patients with BTRE, seizure reduction was 45% at 3 months and 49% at 24 months.[60] These outcomes were similar to 326 patients in the registry who did not have brain tumours. Despite these encouraging results, there was no significant difference in ASM usage in either group throughout the duration of the study. Any potential benefits from VNS need to be weighed against the technical difficulty of MRI scanning in patients with a VNS, as they require

specialist input to turn off the leads prior to the scan. Therefore, VNS should only be used in patients with intractable seizures who have had other oncological treatments explored.

Conclusion

Data on the effects of specific interventions on BTRE are sparse and there are few studies which report on seizure outcomes as the majority of oncological studies concentrate on Survival and/or Quality of Life rather than seizure control. The following recommendations for treatment aim to support clinicians caring for BTRE patients to make informed management decisions. A number of studies have highlighted specific risk factors for the development of BTRE, but in terms of therapy, further research is to needed to establish whether any one of the first line drugs currently used is more effective than any other for BTRE. To date there are no evidence to support the prophylactic use of ASM in BTRE. This review has highlighted the relative dearth of high quality evidence for the management of BTRE and provides a framework for further studies aiming to improve seizure control, quality of life, and indications for ASMs.

Recommendations for treatment

The following treatment recommendations have been written based on the best available evidence. Please see the British National Formulary (BNF) or the British National Formulary for children (BNFC) for further details of the pharmacological treatments outlined.

Incidence of BTRE

• Seizures occur in up to 90% of adult patients with low-grade gliomas and are more frequent than in patients with high-grade gliomas or brain metastases (BM).

• Up to 50% of patients with Brain Tumour Related Epilepsy (BTRE) have intractable seizures and require combination therapy using multiple Anti-Seizure Medications (ASMs) and consideration of non-pharmacological adjunctive therapies.

First line Management

• It is recommended that ASM treatment with levetiracetam or lamotrigine is offered to all patients with primary or metastatic brain tumours who have seizures, even a solitary seizure.

• If treatment with one first line ASM is unsuccessful either because of lack of efficacy or adverse effects, the patient should be switched to an alternative first-line ASM. The dose of the second drug should be gradually increased until the lowest recommended maintenance dose. The first drug should be gradually weaned off.

• Lamotrigine may increase the risk of cardiac arrhythmia mainly in patients over 60 or with heart disease so an ECG should be requested to rule out Left Bundle Branch Block or 2nd or 3rd degree AV block.

Second Line Management

• Combination ASM therapy should be offered where monotherapy is ineffective for seizure control. About 50% of patients with BTRE may continue to have seizures despite 2 or more ASMs at therapeutic doses (Intractable Epilepsy). Patients may safely be treated with multiple ASMs simultaneously to optimise seizure control.

• Second line drugs that can be offered as add-on therapy include carbamazepine, lacosamide, oxcarbazepine, perampanel, sodium valproate, topiramate, zonisamide. There is no evidence for superiority of one drug over the other.

• ASM treatment should revert to the smallest number of ASMs at the lowest effective doses that provides the optimal balance between efficacy and tolerability.

• Wherever possible, enzyme inducing drugs such as carbamazepine and oxcarbazepine should be avoided as they may compromise the efficacy of chemotherapy drugs and other hepatically metabolised drugs. Carbamazepine should also be avoided in patients with a history of AV block.

• Patients should have ECG monitoring prior to prescribing lacosamide (may cause prolonged PR interval and AV block).

ASM withdrawal for patients in remission

• The withdrawal of ASMs in patients with BTRE is controversial, as the presence of a symptomatic tumour is associated with an increased risk of seizure relapse.

• The potential benefits of ASM withdrawal need to be carefully weighed against the risk of seizure recurrence and the potential loss of driving privileges, in a shared decision-making process.

• ASM withdrawal may be considered for patients with stable disease and in patients with tumours associated with a good prognosis who have been seizure free for at least one year.

ASM prophylaxis

• Prophylactic ASM treatment is not recommended for patients with either primary or metastatic tumours and who have not had seizures.

Treatment of the Underlying Brain Tumour

• The first line treatment for patients with gliomas in an operable location and for large symptomatic brain metastases is surgical resection/debulking and this often improves seizure control.

• Radiotherapy and chemotherapy has also been shown to decrease seizure frequency.

Non-pharmacological Management in Intractable BTRE

• Patients with low-grade gliomas who are on surveillance and who have intractable epilepsy causing significant impact on quality of life despite 2 or more ASMs at therapeutic doses should be considered for radiotherapy and chemotherapy, even in the absence of tumour progression.

• Vagal Nerve Stimulation (VNS) should be considered as adjunctive therapy for patients with intractable epilepsy on multiple ASMs who are not being considered for tumour R. ASM therapy should not be withdrawn in patients with VNS.

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Disclosure of Conflicts of Interest

None of the authors have any conflicts of interest to disclose.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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