REVIEW

Seizures and epilepsy in oncological practice: causes, course, mechanisms and treatment

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There are few data available on the causes and mechanistic basis, outcome and treatment of seizures and epilepsy in people with systemic cancer. Seizures and epilepsy in people with cancers other than primary brain tumours are reviewed here. Articles published in English, which discussed the neurological manifestations and complications of cancer and its treatment, were searched and information on the frequency, aetiology, and course of seizures and epilepsy was extracted. The frequency, aetiology and outcome of seizure disorders in patients with cancer differ from those in the general population. Intracranial metastasis, cancer drugs and metabolic disturbances are the most common causes. Infections, cerebrovascular complications of systemic cancer and paraneoplastic disorders are among the rarer causes of seizures in patients with neoplasms. Several drugs used in the treatment of cancer, or complications arising from their use, can trigger seizures through varied mechanisms. Most drug-induced seizures are provoked and do not require long-term treatment with antiepileptic drugs.

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Epilepsy and seizures are among the most common neurological conditions affecting all ages. The overall incidence of epilepsy in developed countries is about 50/100 000 persons/year, and the cumulative lifetime incidence of seizures is over 10%.[1 2] Likewise, cancer, another common medical condition, affects one in three people overall. In all, over 270 000 new cases of cancer were registered in the UK in 2000. Cancer is the cause of 26% of the deaths in the UK, and outnumbers heart disease as a cause of death.[3] Seizures and epilepsy may therefore occur, coincidentally or otherwise, in some people with cancer, and the cancer may influence the incidence, treatment and prognosis of seizures and epilepsy.

We recently reviewed the comorbidity of cancer in people with epilepsy.[4] Here we discuss the causes, outcome and treatment of seizures and epilepsy in people with neoplasms. This review focuses on the occurrence of seizures and epilepsy in people with systemic cancer, and excludes brain tumours as these have been discussed elsewhere.[5 6] Mechanistic considerations involving cancer drug-induced seizures are discussed in some detail, as these have not received much attention so far. Neurologists should be aware of the unique set of causes of seizures in people with cancer, as well as their outcome and treatment, especially as the occurrence of seizures in a patient with cancer often prompts neurological consultation.

SEARCH STRATEGY

PubMed and Medline were searched for articles that discussed the neurological manifestations and complications of cancer and its treatment. These were then searched for mention of seizures and/or epilepsy. Information on the frequency, aetiology, mechanisms, treatment and course of seizures, and epilepsy was extracted from these articles.

INCIDENCE OF SEIZURES IN PATIENTS WITH CANCER

An estimation of the frequency of seizures in people with cancer ideally requires community-based data, which are lacking. Data from specialist cancer units are available, but there are limitations to extrapolating data from such centres. When all types of neurological problems among patients with cancer were analysed at a specialist cancer centre, seizures were found to occur in 13% of all patients with cancer and to account for approximately 5% of all neurological manifestations.[7] Half of the seizures were attributed to intracranial metastasis, and most of the remainder to metabolic disturbances. As a considerable proportion of seizures among adults with systemic cancer arise due to intracranial metastasis, cancer sites that would be expected to be commonly associated with seizures include lung, breast, skin (malignant melanoma) and colon.[7]

Children with cancer seem to have a higher incidence of seizures than adults.[8] Most seizures occur in children with acute leukaemias, in whom these are provoked by drugs used during bone marrow transplantation (BMT).[9 10] Other oncological conditions associated with seizures include lymphomas, neuroblastomas and sarcomas.[8 11]

CAUSES OF SEIZURES IN PATIENTS WITH CANCER

Seizures that occur in patients with cancer may have a variety of causes, including brain parenchymal and meningeal metastasis, the administration of cytotoxic chemotherapy and toxic–metabolic encephalopathy. Several other rare conditions, some of which are unique to cancer, may also be responsible for seizures. These are reviewed later. Additionally, any condition that produces

Abbreviations: BMT, bone marrow transplantation; CNS, central nervous system; EEG, electroencephalograph; MRI, magnetic resonance imaging; 5-FU, 5-fluorouracil; MUD, matched unrelated donor

seizures in the general population may also cause seizures in people with cancer.

Intracranial metastasis

Brain metastases are less likely than primary brain tumours to cause seizures; rather, headaches (due to raised intracranial pressure) and changes in behaviour and mental status are the more common manifestations, probably because intracranial metastasis often tends to be multiple and to involve the posterior fossa.[12 13] Lung cancer (both non-small cell and small cell) is the most common cancer associated with metastasis presenting with seizures, although they may also arise from the breast, skin and colon cancers.[14] The time interval between diagnosis of the primary tumour and occurrence of seizures due to metastasis depends on the propensity of the primary tumour to metastasise to the brain.[13] Central nervous system (CNS) metastases occur early, often on presentation, in lung cancers and malignant melanoma, but may be delayed by as much as 2–3 years in breast cancers. Seizures are usually a manifestation of parenchymal metastasis, but may also be a feature of leptomeningeal metastasis.[15]

The occurrence of a seizure in a patient with cancer should almost always prompt imaging studies with gadolinium-enhanced magnetic resonance imaging (MRI) to rule out brain metastasis. However, some brain masses presenting with seizures or other neurological manifestations in patients with systemic cancer may be non-neoplastic in nature.[16] Conditions such as brain abscesses, granulomatous conditions and focal demyelination may mimic brain metastasis in their clinical and radiological manifestations.

Drug-induced seizures

When seizures occur for the first time in patients under treatment for cancer, the possibility of drug-induced seizures should be considered. Indeed, seizures represent the dose-limiting toxicity of many cancer drugs. A high frequency of seizures has been reported in phase 1 and 2 clinical trials of some cancer drugs, especially as high doses of the drugs are used to determine the range and limits of toxicity.[17] In routine clinical practice, however, seizures are more likely to be encountered as a manifestation of drug toxicity when high doses are given as part of myeloablative treatment in preparation for BMT, or in the presence of renal or hepatic disorders (when routine dosages of the drugs can lead to toxicity). Few authors have proposed definite criteria for labelling seizures as drug induced. These include (1) development of encephalopathy and seizures during or shortly after administration of the drug, (2) exclusion of other metabolic and structural factors and (3) exclusion of seizures produced by concomitant drugs.[18 19]

Most drug-induced seizures occur within hours or days of cancer drug administration. However, they may occur after several days when the half life of the drug is prolonged as a result of impaired hepatic or renal clearance.

Cisplatin

Cisplatin is used for the treatment of bladder, ovarian, head and neck, brain and lung neoplasms. The occurrence of seizures is a well-documented, albeit rare, manifestation of cisplatin toxicity.[20] Focal or generalised seizures may occur in conjunction with cortical blindness, acute confusional state and agitation, and, in some instances, mutism and elevated blood pressure, usually 5–15 days after administration of cisplatin. The imaging correlate of this condition is white matter lesions underlying the occipital cortices that resolve over a few days, referred to as the ''reversible posterior leucoencephalopathy syndrome''. Electroencephalographic (EEG) examination may disclose a diffuse encephalopathic pattern, focal slow-wave activity, electrographic status epilepticus or periodic lateralised epileptiform discharges.[20 21]

An association has been noted between the occurrence of cisplatin-induced seizures and electrolyte disturbances, particularly hypomagnesaemia, hypokalaemia and hyponatraemia, and, in some instances, renal failure.[21] These electrolyte disturbances may be manifestations of the renal tubular toxicity of cisplatin, and their pathogenic relevance is unclear. Hypomagnesaemia produces a proconvulsant state in the brain and should be corrected.[22] The presence of renal failure leads to impaired clearance of cisplatin, resulting in high blood and tissue levels, causing seizures. The method of administration of cisplatin may also be relevant; a number of reported cases with seizures have received a continuous infusion over 2–5 days rather than for short durations. [20] It has been shown that levels of the drug peak towards the end of a prolonged infusion period as opposed to an immediate peak after bolus administration.[23] In addition, the half life of cisplatin after infusion can range from 30 to 107 h compared with about 45 min after bolus administration, accounting for the occurrence of neurotoxicity 5–15 days after administration.[24] Finally, the administration of cisplatin by the intra-arterial route for head and neck and brain neoplasms is associated with seizures in up to 20% of cases.[25]

Busulphan

Busulphan is an alkylating agent traditionally used in the treatment of chronic myeloid leukaemia and in high doses in the myeloablative regimen of haematopoietic BMT, which is more commonly associated with seizures.[26 27] Generalised tonic–clonic and/or myoclonic seizures may occur during or soon after the administration of the drug. EEG examination may disclose interictal polyspikes in association with a diffuse encephalopathic pattern.[27] As with several other alkylating agents, busulphan crosses the blood–brain barrier with relative ease. The occurrence of seizures is dose dependent.[26] It is therefore likely that high levels of the drug after crossing the blood–brain barrier produce transient and self-limiting excitotoxic neuronal injury. Considerable interindividual variability occurs in the pharmacokinetics of busulphan, and this may explain why some people are predisposed to seizures.

Chlorambucil

Chlorambucil is another alkylating agent of the nitrogen mustard type used in the treatment of chronic lymphocytic leukaemias and low-grade non-Hodgkin's lymphomas. Seizures have been described in the context of inadvertent overdosing (usually at least 1.5 mg/kg), after pulse doses and after the use of high-dose chlorambucil as preparative treatment for BMT.[28 29] Children are particularly susceptible to seizures, perhaps because of an age-dependent vulnerability or altered pharmacokinetics of the drug.[28] Seizures associated with chlorambucil take the form of fragmentary or multifocal myoclonus or generalised tonic–clonic convulsions.[29] EEG studies performed after overdosage typically show a mildly encephalopathic pattern in addition to 2–3 Hz generalised spike-wave discharges which ameliorate gradually over several days to weeks.

5-Fluorouracil

The antimetabolite 5-fluorouracil (5-FU) is widely used as a chemotherapeutic agent in the treatment of colorectal, breast, and head and neck cancers. Neurological toxicity in the form of encephalopathy and seizures has rarely been described.[18 19 30] Published accounts of neurological toxicity, however, vary in terms of biochemical and pathological basis. A multifocal leucoencephalopathy, characterised by cerebellar ataxia, somnolence, dementia, encephalopathy and, rarely, seizures, can develop 15–20 weeks after the initiation of treatment with

5-FU. MRI shows multiple white matter lesions. Clinical and imaging abnormalities may improve with corticosteroids. In some reports, the administration of 5-FU was combined with levamisole; it is therefore possible that the immunomodulatory effects of levamisole are responsible for the condition.[30] Another report described the occurrence of encephalopathy and seizures with hyperammonaemia and lactic acidosis after high-dose 5-FU and leucovorin administration in 16 of 280 patients receiving this regimen.[18] The toxicity of 5-FU has also been linked to an inherited deficiency of the enzyme dihydropyrimidine dehydrogenase due to mutations in the dihydropyrimidine dehydrogenase gene, of which at least 23 different polymorphisms exist.[31] This enzyme is involved in the catabolism of 5-FU, and its deficiency leads to toxic accumulation of the drug. The most common mutation, a splice-site mutation (c.1905+1G→A), is associated with severe bone marrow suppression.[32] In one report, however, the c.1601G→A polymorphism was associated with multiorgan failure, including seizures, myoclonus and encephalopathy, after 5-FU administration.[33] Other polymorphisms may underlie some of the neurological toxicity syndromes described above.

Methotrexate

Methotrexate, another antimetabolite, is a competitive inhibitor of the enzyme dihydrofolate reductase. It is used in the treatment of acute lymphocytic leukaemia, non-Hodgkin's lymphoma including primary CNS lymphoma, trophoblastic neoplasms and breast carcinoma. In addition, intrathecal methotrexate is used in the treatment of carcinomatous meningitis and the prophylaxis of CNS involvement in acute leukaemia.

Seizures have been reported after the administration of methotrexate in two situations. One is the accidental overdose of methotrexate through the intrathecal route.[34] Seizures and encephalopathy occur immediately after administration. Focal neurological deficits may also be encountered. MRI is normal in such cases, although diffusion-weighted imaging may show areas of restricted diffusion that eventually resolve.[35] Seizures can also occur as a delayed sequel to methotrexate administration.[36] This may occur several months after initiation of treatment, and is characterised by rapid cognitive decline due to a subcortical encephalopathy. In most cases reported, methotrexate use has been accompanied by whole brain radiotherapy, and the combination of the two is thought to be involved in the aetiopathogenesis of this specific syndrome. The risk of seizures seems to be highest when both intrathecal and intravenous methotrexate are given in combination with cranial irradiation.[37] However, the use of methotrexate alone has also been noted to produce a similar neurological syndrome.[36] Children seem to be particularly at risk of developing this syndrome, although the frequency quoted depends on the techniques used to detect it and on the doses of methotrexate used; the rate may be as high as 55%.[38 39] The condition is characterised by subcortical leucoencephalopathy involving the periventricular and subcortical ''U'' fibre regions, visible on neuroimaging as T_2 and fluid-attenuated inversion recovery image hyperintense signals in addition to ventricular dilatation and cortical atrophy.[36] Occasionally, calcification may also be seen in the subcortical locations. These changes are thought to be ischaemic in origin; support for a vascular basis comes from a mineralising microangiopathy shown in pathological specimens obtained on autopsy of those who received methotrexate alone or in combination with radiotherapy in life.[40]

Interferon α

Seizures occur in 1–4% of patients given interferon α, which is sometimes used in the management of multiple myeloma and hairy cell leukaemia.[41] The toxicity has been attributed to mechanisms such as disruption of the blood–brain barrier and consequent vasogenic brain oedema, and lowering of the seizure threshold through an effect on neuronal excitability mediated via cytokines.[41 42] Interferon α-2a administration has been reported to produce self-limiting photosensitive seizures in association with a photoparoxysmal response on the EEG.[43]

Cyclosporin A

Cyclosporin A is widely used as an immunosuppressive agent in the prevention and management of graft rejection and graft versus host disease after BMT (for the treatment of leukaemias). Seizures are an important feature of cyclosporin neurotoxicity, which manifests as a reversible posterior leucoencephalopathy, similar to that caused by cisplatin (mentioned above). Cyclosporin levels are usually, but not necessarily, high during such episodes.[44] Although seizures due to cyclosporin neurotoxicity may be acutely repetitive and may present as status epilepticus, they do not usually recur once the drug is withdrawn and reinstituted in lower doses.[45] However, there are some reports of recurrent unprovoked seizures after cyclosporin neurotoxicity.[44] Mesial temporal sclerosis may develop after posterior leucoencephalopathy due to cyclosporin, but the cause–effect relationship remains controversial.[46 47]

Seizures due to cyclosporin neurotoxicity may be mediated through endothelial damage through the elaboration of endothelin-1 and reduction in nitric oxide concentrations or mitochondrial aberrations.[48] There is also evidence from experimental studies for a direct effect of cyclosporin A on neuronal excitability.[49]

Other cancer drugs

Several other cancer drugs have anecdotally been associated with seizures. A comprehensive list of such drugs can be found elsewhere and includes ifosfamide, L-asparaginase, BCNU, cyclophosphamide, etopuside (VP-16), dacarbazine, vincristine, mechlorethamine, procarbazine, paclitaxel, fludarabine, cladribine, pentostatin and tenoposide.[50 51] The administration of certain other drugs to ameliorate cancer-related or cancer chemotherapy-related complications may also cause seizures. Examples of these include octreotide (a diarrhoea drug), odanseteron (an antiemetic agent) and imipenem (an antibiotic).[50–3]

Metabolic conditions

It is important to recognise toxic–metabolic encephalopathy as a cause of seizures, as the appropriate treatment is correction of the underlying metabolic defect rather than institution of epilepsy drugs. Metabolic disturbances may cause a substantial proportion of seizures in oncological practice, although it may not be possible to identify the exact underlying cause.[7 9] Many metabolic disturbances may be drug induced. For instance, both cyclophosphamide and ifosfamide cause inappropriate vasopressin secretion and consequently hyponatraemic seizures, bisphosphonates cause hypocalcaemic seizures, and cisplatin may result in hypomagnesaemia and seizures.[20 54–56] Rarely, seizures may be the presenting or predominant manifestation of tumours such as insulinoma and phaeochromocytoma.[57 58]

Neurological paraneoplastic syndromes

Paraneoplastic disorders of the nervous system are rare non-metastatic complications of cancer, often diagnosed on the basis of a characteristic clinical picture and the presence of specific antineuronal antibodies.

The occurrence of seizures is an important feature of limbic encephalitis, which is a restricted expression of paraneoplastic encephalomyelitis. It is characterised by complex partial seizures or localisation-related status epilepticus in association

with prominent memory and behavioural disorders. Seizures are recurrent, and often refractory to medical treatment. In a series of 50 patients with paraneoplastic limbic encephalitis, seizures were among the presenting manifestations in 12% of cases and occurred later during the course of the illness in 50% of cases.[59] Rarely, seizures may be the predominant manifestation of the paraneoplastic syndrome.[60] The symptoms may antedate detection of the neoplasm by up to 3 years, although occasionally the neoplasm may be diagnosed only at autopsy. Imaging may show high-signal areas in the anteromesial temporal lobes and/or the basifrontal lobes. There is an association with antibodies to neuronal nucleoli, including the anti-Hu and anti-Ma-2 antibodies.[59] Histological findings at autopsy may or may not show active inflammatory abnormalities; rather, gliotic and atrophic changes in the amygdala, hippocampus and other temporal lobe structures may overshadow other histological features, presumably reflecting the long duration of the pathological process. Cancers that are commonly associated with limbic encephalitis include small-cell lung carcinoma and testicular tumours.[59] Equally rare and disappointing from the treatment standpoint is the clinical condition comprising epilepsia partialis continua with noticeable focal lesions, involving the frontal motor cortex, which has anecdotally been associated with anti-Hu antibodies.[61] This is also presumably a focal form of paraneoplastic encephalomyelitis, linked to small-cell carcinoma of the lung. Histopathological examination, when performed, shows focal or multifocal perivascular lymphocytic infiltrates in the cortex and brain stem.

Cerebrovascular complications of cancer

Stroke is the second most common brain disorder (after metastasis) identified at autopsy in patients with cancer.[62] In one series of 96 patients with systemic cancer who developed a stroke, seizures were found to occur in 8% of the patients.[63] As discussed later, a variety of stroke syndromes may manifest with seizures.

Venous sinus thrombosis often presents with seizures, especially when occlusion leads to the development of cerebral parenchymal infarcts or haemorrhages. It may occur because of occlusion of the venous sinuses by leukaemic infiltrates, and rarely because of invasion of sinuses from dural metastasis from solid tumours or because of the administration of cancer drugs, in particular, L-asparaginase, when used in the induction therapy of acute lymphocytic leukaemia.[64] L-asparginase predisposes to a prothrombotic state via inhibition of synthesis of proteins involved in the coagulation cascade, including antithrombin III, protein C and protein S.

Parenchymal brain haemorrhages may cause seizures in association with headaches, focal neurological deficits and neurological obtundation. They are associated with certain cancer types, including acute myeloid leukaemia (where coagulation defects predispose to haemorrhage), and with malignant melanoma and choriocarcinoma, both of which give rise to haemorrhagic cerebral metastasis.[62 63]

A rare disorder, intravascular lymphoma (either B cell or T cell type), pathologically characterised by involvement of the intravascular structures by tumour cells, produces a clinical syndrome of seizures, encephalopathy and focal neurological deficits.[65] Another rare but characteristic disorder, thrombotic microangiopathy, manifests with seizures, encephalopathy and multiple deficits along the CNS axis, in addition to thrombocytopenia and haemolytic anaemia, and is associated with advanced mucin-producing adenocarcinoma.[66]

CNS infections

The incidence of CNS infections is increasing as more effective cancer treatments become available. CNS infections complicating cancer have been classified according to the anatomical predilections of the infecting organisms.[67] In general, seizures are manifestations of those infectious processes that involve the parenchymal cortex (eg, viral infections involving the limbic and neocortex caused by herpes simplex, human herpes virus 6 and 7 and focal mass lesions due to aspergillosis, nocardiosis and toxoplasmosis) as opposed to those that involve the meninges or the subcortical structures. Meningitic infections (eg, cryptococcal meningitis) and subcortical disorders (eg, progressive multifocal leucoencephalopathy) rarely produce seizures.

Insults to the limbic cortex are often associated with seizures and with convulsive and non-convulsive status epilepticus; these may be the result of human herpes virus 6 and 7 infection, herpes simplex infection, paraneoplastic limbic encephalitis and autoimmune limbic encephalitis. Human herpes virus has recently been recognised as being transmitted through BMT.[68] In addition, it has been anecdotally implicated in fulminant cutaneous reactions that complicate the administration of epilepsy drugs (see below).[69]

Cranial irradiation

Seizures may be among the presenting features of both acute radiation encephalopathy and delayed radiation necrosis.[70 71] Rarely they may be the dominant manifestation, and in such cases they are refractory to medical treatment.[70] A rare post-irradiation syndrome consists of medial temporal lobe and pituitary necrosis with ensuing seizures and hypopituitarism after radiation therapy for nasopharyngeal carcinoma.[72] Cranial irradiation may also lead to the development of cavernous haemangiomata as a delayed sequel.[73] These vascular malformations are typically associated with intractable epilepsy due to repeated minor haemorrhages.

INVESTIGATIONS AND TREATMENT OF SEIZURES IN ONCOLOGICAL PRACTICE

The timing of seizure occurrence in relation to oncological diagnosis and institution of chemotherapeutic treatment may have some aetiological implications. However, temporal trends in the incidence of seizures do not provide rigid distinctions in aetiology as a number of disparate conditions are known to cause their occurrence (table 1). Seizures that occur during or soon after institution of cancer chemotherapeutic treatment are likely to be drug induced. Seizures due to intracranial metastasis or CNS infections occur later, but the timing of occurrence may vary according to the primary cancer site.

Although aetiological distinctions based on timing of seizure occurrence seem credible, these should not influence the investigative examination of seizures in oncological practice. Instead, a standard and rigorous protocol for examination is recommended. The most important investigation is contrast-enhanced MRI, which incorporates contemporary sequences and protocols—in particular, the fluid-attenuated inversion recovery images. This is primarily directed towards establishing the presence of parenchymal or leptomeningeal involvement by cancer, and of other neurological complications such as cerebrovascular and infectious disorders. Concomitantly, a comprehensive metabolic investigation including serum or cerebrospinal fluid drug assays, if available, should be undertaken. Many drug assays, apart from cyclosporin A, are not available in routine clinical practice. Further investigation, particularly if investigations thus far are non-contributory, includes a large-volume lumbar puncture that is then submitted for cytological examination for tumour cells indicative of leptomeningeal cancer and microbiological and immunological examinations for infections.

Table 1 Temporal trends in aetiological considerations of new-onset seizures in patients with systemic cancer

Time period	Aetiological condition
Seizures before diagnosis of tumour	Paraneoplastic limbic encephalitis Paraneoplastic encephalomyelitis Endocrine tumours Primary cancers with high propensity to CNS metastasis: malignant melanoma, lung carcinoma
Seizures occurring during administration of cancer chemotherapy	Drug-induced seizures Metabolic disorder (mostly drug induced)
Seizures occurring few weeks to months after chemotherapy	CNS infections Intracranial metastasis
Seizures occurring many months to years after chemotherapy	Intracranial metastasis CNS infections Radiation necrosis Paraneoplastic disorders Methotrexate-cranial irradiation leucoencephalopathy
Seizures occurring several years after tumour diagnosis	Intracranial metastasis Radiation necrosis Radiation-induced tumours/ cavernous haemangiomata CNS infection Paraneoplastic disorders

CNS, central nervous system.

Table 2 Characteristics and aetiological correlations of new-onset seizures in patients with cancer

Syndromic characteristic	Aetiological condition
Isolated generalised tonic–clonic seizures/seizure clusters	Most drug-induced seizures (see text for discussion on each agent) Metabolic encephalopathy Endocrine tumours Intracranial metastasis CNS infections Viral encephalitides Parenchymal space-occupying infections Cerebral venous sinus thrombosis
Myoclonic seizures	Busulphan
Photosensitive seizures	Interferon α
Multiple focal seizures/varying semiology	Intracranial metastasis Multifocal parenchymal infections Paraneoplastic encephalomyelitis
Status epilepticus	Cyclosporin Toxic-drug overdose Drug-induced seizures in the setting of impaired clearance
Non-convulsive status epilepticus	
(a) Generalised	Ifosfamide
(b) Complex partial	Paraneoplastic limbic encephalitis Limbic encephalitis due to herpes virus Cyclosporin
Epilepsia partialis continua	Paraneoplastic encephalomyelitis Venous sinus thrombosis with venous infarct
Unprovoked recurrent seizures, easily controlled with epilepsy drugs	Methotrexate-radiation leucoencephalopathy Unprovoked seizures after cerebrovascular accident CNS infections
Intractable complex partial seizures/epilepsy	Paraneoplastic limbic encephalitis Delayed radiation necrosis Herpes virus-induced encephalitis

CNS, central nervous system.

Box 1 Practical options for institution and maintenance of epilepsy drug treatment in patients with systemic cancer

- Lorazepam (2 mg four times daily; adult dose) may be given orally from 1 day prior till 1 day after administration of high-dose busulphan for myeloablative treatment before bone marrow transplant.
- No treatment is required for isolated seizures associated with cancer drug administration or metabolic encephalopathy.
- Parenteral lorazepam (0.05 mg/kg, slow intravenous) may be given as abortive treatment of prolonged or repetitive seizures associated with cancer drug administration or metabolic encephalopathy.
- In the case of repetitive seizures due to reversible posterior leucoencephalopathy syndrome, anticonvulsants may be given for a few weeks or months.
- For all other conditions in which a structural lesion is detected on imaging studies in patients with new-onset seizures, prolonged treatment with a non-enzyme-inducing epilepsy drug is indicated.
- Enzyme-inducing antiepileptic drugs may cause increased metabolism of anti-cancer drugs and higher doses may therefore be required.

Acute treatment of seizures

Several considerations arise in the choice of antiepileptic drugs in the management of seizures in oncological practice. As most seizures are acute symptomatic, a drug with rapid onset of action is usually required. For this purpose, some antiepileptic drugs can be given as a loading dose if required. Several antiepileptic drugs have parenteral formulations available for acute loading; this may be particularly desirable in view of the need for rapid onset of action and the fact that absorption of orally administered antiepileptic drugs may be compromised by the toxic effect of cancer drugs on the gastrointestinal mucosa. Another consideration is the range of drug interactions between antiepileptic drugs and cancer drugs. These have been the focus of much attention lately.[4 74] Most cancer chemotherapeutic agents interfere with the absorption of antiepileptic drugs by causing damage to the intestinal mucosa, leading to reduced serum levels of antiepileptic drugs and potentially compromising their efficacy. On the other hand, serum levels of several cancer chemotherapeutic drugs are reduced by the prior, chronic administration of hepatic enzyme-inducing antiepileptic drugs, including phenytoin, phenobarbital, carbamazepine and, to a lesser extent, oxcarbazepine and topiramate. Although not conclusively shown in clinical practice, such interactions may impair the efficacy of cancer chemotherapeutic agents.[74] One final consideration in the choice of antiepileptic drugs is the range of adverse effects of antiepileptic drugs that are specific to the cancer population. For instance, the use of phenytoin for primary and metastatic brain tumours has been associated with a high incidence of anticonvulsant hypersensitivity syndrome.[75] This is particularly the case when cranial irradiation is used for the treatment of brain tumour; in such cases, the rash begins at the stage of radiotherapy, but subsequently progresses to erythema multiforme major and subsides when phenytoin administration is withheld. Similarly, the use of valproate in association with certain cancer chemotherapeutic agents such as cisplatin results in enhanced haematological toxicity, partly due to the precipitation of

toxicity of the cancer chemotherapeutic agent due to hepatic enzyme inhibition and partly due to the propensity of valproate to cause thrombocytopenia.[76]

It is current practice to use benzodiazepines in the prophylaxis of drug-induced seizures when indicated (box 1). One situation in which their use is particularly recommended is during conditioning treatment for BMT with busulphan. The frequency of seizures in response to high-dose busulphan has prompted the use of anticonvulsant prophylaxis before, and until 24 h after, busulphan administration. The initial recommendation of phenytoin-sodium use has been superseded, as phenytoin was found to increase the clearance of busulphan, thereby decreasing its steady-state concentration.[77] Concerns that this drug interaction would lead to reduced efficacy of the preparative regimen for BMT led to the use of other anticonvulsants, including oral and intravenous clonazepam, lorazepam, diazepam, phenobarbital and clobazam.[78–80] Lorazepam is used most often and offers the advantages of both lack of any drug interaction and an antiemetic action.[80] It is administered orally before busulphan treatment and is continued until 24 h after the last dose.

Long-term epilepsy with drug treatment

In most circumstances, long-term treatment with antiepileptic drugs is not required (fig 1), but, when indicated, control of seizures is usually good. As cyclosporin neurotoxicity produces structural aberrations, albeit transient, antiepileptic drugs may be given for a few months. Seizures due to brain metastasis, recurrent unprovoked seizures as a result of methotrexate-cranial irradiation-induced leucoencephalopathy, rare instances of late seizures after cyclosporin neurotoxicity and late seizures complicating cerebrovascular or infectious complications in patients with cancer warrant long-term antiepileptic drug treatment. In such situations, the use of enzyme-inducing antiepileptic drugs is best avoided. Levetiracetam, gabapentin, lamotrigine, topiramate and pregabalin are antiepileptic drugs with no known interactions with cancer chemotherapeutic agents, although experience with their use in people with cancer is limited. When epilepsy occurs coincidentally with cancer, the possibility that drug interactions between newly administered cancer chemotherapeutic agents and antiepileptic drugs may impair seizure control must be considered.[81] The measurement of serum levels of antiepileptic drugs is indicated in such instances.

The outcome of seizures due to brain metastasis, as opposed to those due to primary brain tumours, has not been adequately documented, perhaps owing to the limited survival of people with this condition. Although generalised seizures are easily controlled with appropriate doses of single antiepileptic drugs, focal seizures may continue to occur despite adequate treatment. Oncological treatment, whether surgery or irradiation and possibly corticosteroids may ameliorate the seizure disorder to a certain extent. The prophylactic administration of antiepileptic drugs to individuals with brain metastasis has been conclusively shown to be of no benefit.[82] It remains to be seen whether any of the newer epilepsy drugs would be useful in the prevention of seizures due to intracranial metastasis.

The issue of surgical management of intractable epilepsy that occurs coincidentally with cancer may arise rarely. In such situations, estimates of the oncological survival should guide the decision to proceed to surgery. In view of the limited survival time of people with certain cancers, epilepsy surgery is

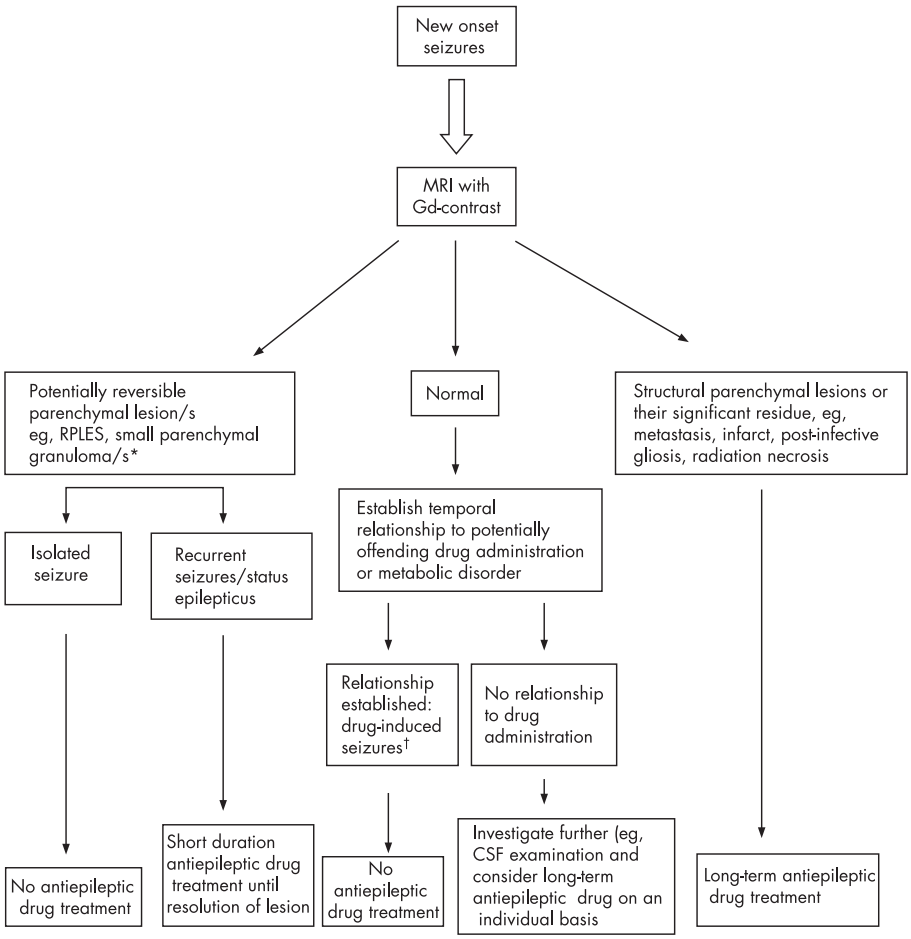

Figure 1 Flow chart depicting suggested epilepsy drug (ED) strategy in the event of new-onset seizures in patients with cancer. CSF, cerebrospinal fluid; Gd, gadolinium; MRI, magnetic resonance imaging; RPLES, reversible posterior leucoencephalopathy syndrome. *Small granulomatous infections such as toxoplasmosis or neurocysticercosis usually do not leave residual scars. †The absence of other identifiable structural or metabolic factors as determined by gadolinium-enhanced MRI and metabolic screen in addition to drug levels in selected cases is required to establish a firm diagnosis of drug-induced seizures.

best avoided. However, as most childhood acute leukaemias and many lymphomas are now essentially curable, surgical management of intractable epilepsy may be actively pursued in such cases.[47]

CONCLUSIONS

The variety of ways in which seizures may be caused by malignancy and its treatment are important to both oncologists and neurologists. Current evidence regarding the cause of new-onset seizures and epilepsy in people with cancer is based on studies from hospitals, mostly of single cases or small series. Further research, particularly well-conducted prospective studies, is required. Similarly, although the appreciation of several interactions between cancer drugs and antiepileptic drugs is growing, the adverse effect, if any, on cancer outcome and survival needs to be studied in multicentre studies, given the rarity with which patients with cancer require long-term epilepsy drug treatment. Finally, clinical trials of newer antiepileptic drugs including levetiracetam, gabapentin and pregabalin in people with cancer may help clarify their safety and efficacy in this population.

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