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Wolfgang Grisold

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Margrethe Raspotnig, Cecilie Totland, Anette Storstein, Christian Vedeler

Neurologic Complications in Multiple Myeloma and Plasmacytoma
Roser Velasco, Jordi Bruna

Neurologic Complications of Hematopoietic Stem Cell Transplantation
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Imprint
Editorial

EANO is the European organisation that represents all medical and scientific disciplines involved in the diagnosis and treatment of tumours of the nervous system. It exists to stimulate collaboration and interaction for those interested in neuro-oncology and provides educational activities through biannual congresses, biannual educational events via the website, and also by means of its journal and magazine. This is what our EANO website says, and I think I have a few points to add. We are multidisciplinary and multiprofessional, and we are increasingly aware of patient advocacy and patient input. We have renewed the scientific board. Dr Weller is EANO’s co-editor for the joint scientific journal with SNO, Neuro-Oncology. Dr Soffietti is the editor for EANO’s neuro-oncological online magazine (http://www.kup.at/journals/eano/), which had an excellent start.

The EANO has developed into a modern society engaged in many activities, which are taken care of by individual members of the board. One of the main activities is education, which covers several aspects ranging from fellowships and department visits to travel grants. We have already awarded one successful fellowship and are about to nominate the second EANO fellow in the near future. The EANO is actively involved in the education committee of ECCO and has a permanent member in the accreditation committee of ECCO’s ACOE. In the past 2 years, EANO has participated in an EU project on ECCO oncoides (http://www.ecco-ory.eu/ondcoides), which covers 4 neuro-oncological topics and can be downloaded on the ECCO website. We are aware of our commitment to ECCO as the largest European Cancer Organisation and we are successfully implemented in several ECCO activities.

EANO not only organises a joint educational meeting with the EORTC but also shares many contacts. As the EORTC is involved in many studies and scientific activities this is an invaluable aspect.

The growing partnership with SNO has enabled us to set up travel grants and conjoint scientific workshops for the SNO and EANO meetings jointly: this is a big step for future co-operations, in addition to the common scientific journal, Neuro-Oncology (http://neuro-oncology.oxfordjournals.org/). Informal talks with representatives from the neuro-oncology section of the American Academy of Neurology (AAN) might indicate the need for future cooperation.

The gate to education is the EANO website (www.eano.eu), which not only provides news and communication but also regular web feeds, cases of the month, and, since 2011, every EANO member has free access to Neuro-Oncology, a high-impact scientific journal. This not only grants EANO members access to scientific papers of high quality but also a platform for publication.

In Maastricht, we decided to launch an open-access magazine on neuro-oncology, the EANO’s online magazine, whose third edition has just been published and which is edited by Riccardo Soffietti. Its download numbers are astonishing (Figure 1) and the purpose of an educational journal for neuro-oncology is to provide a forum for the exchange of ideas and information among professionals in the field. The three most frequently downloaded publications so far are:


Figure 1. Downloads of single PDFs per month of the EANO Magazine (September 2011 until mid-April 2012). The three most frequently downloaded publications so far are:

cology is met. In addition, it also allows us to spread society news, cases, and information on ongoing studies.

The scientific committee has several tasks. A new scientific committee has been active since 2011, the other main task is the creation of the scientific programme for the next EANO congress in Marseille. Beatrice Melin and Wolfgang Wick are successfully engaged in this and have support from the board, the scientific committee, and our PCO, the Vienna Medical Academy (http://www.medacad.org/vma/). Marseille will be the 10th biannual congress in a fabulous location: it will be composed of educational sessions, plenary lectures, free oral presentations and posters, as well as important side meetings with other societies, the industry and national societies, and equally important personal talks and networking. The next EANO meeting is being planned for October 2014 and will take place in Torino, Italy.

Meetings at a two-year interval are not enough, at least for neuro-oncology. This motto has already been used twice for a joint EANO-EORTC meeting, and the last successful meeting took place in Bucharest in 2011. This meeting fulfilled the educational expectations and encouraged EANO to proceed with this type of meeting. The location of these educational meetings serves the spread of neuro-oncology in the area of former Eastern Europe as well. The next educational meeting will take place in 2013 in Prague, and it will be even more powerful because ESMO will join in as a partner. This is a big move toward our goal to spread knowledge and education in the field of neuro-oncology, and it seems that general oncology is increasingly aware of the role of neuro-oncology.

A lot of important but unseen work is done that is required for a smooth organisation. Our secretariat in Holland, personified by Philomène Klomp, is involved in many structural activities that a society needs, and also helps that our plans and ideas materialize. This includes not only membership services but also website administration, office work, and exchange with our PCO, with ECCO as well as other societies. Last but not least, EANO attracted interested persons and established many contacts with its booths both at the ECCO meeting in Stockholm and at the World Federation of Neurology Meeting 2011 in Marrakech (Figure 2). In perseverance of the EANO special meeting for Eastern Europe and North Africa, which took place in Maastricht, another regional meeting will be held in Marseille. Closely related to the office is the work of our treasurer. In Europe, we are facing many changes with regard to the practice of accreditation, cooperation with pharmaceutical companies, and changing laws on VAT and taxation of congresses and societies.

Hanneke Zwinkels takes care of the affairs of nurses and related health groups and also connects with European oncology nurse associations and patient organisations.

One of our portfolio holders is involved in project management. Projects are important tasks of a society, but having an idea is often not sufficient. To define and calculate a project, to estimate its value and viability, and to accompany its move into reality is an important task. For this reason, a person responsible for project development has been appointed. One important project development could be the evolution of a neuro-oncology...
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curriculum for Europe, which may be helpful for several countries. EANO is a dynamic society and we will be glad to receive suggestions and ideas of projects, which could be important for the tasks of EANO.

Several of our board members will reach the end of their office terms in 2012, and some new board members will be elected during the Marseille meeting, which will guarantee the continuation of EANO’s mission and work. The board has already nominated Dr Riccardo Soffietti as the president-elect for 2013–2014 and, in this position he is presently involved in all major decisions.

Is EANO a Political Organisation?
In many ways yes, as it is aiming to bring forward neuro-oncology in order to improve the fate of neuro-oncologic patients. This improvement cannot be achieved by research and science alone, it requires manpower, education, as well as devotion, and neuro-oncology needs a fixed place in the medical community. In the past, during my tenure as president of a European neurological society, I was asked by board members if there was any need for neuro-oncology at all. I am sure these persons have already changed their mind but there is still a lot to do. In the global world, the World Federation of Neurology does not have an own research group on neuro-oncology, in the UEMS several attempts to create a multidisciplinary joint committee on neuro-oncology have so far failed, and in many European countries neuro-oncology does not exist as a multiprofessional and multidisciplinary speciality. This is what we have to aim at in the near future, and the overall aim to improve available neuro-oncological services for all patients.

As this will be my last column as the EANO president, I would like to thank the EANO for having given me the opportunity to be the president in these exciting times and for supporting me in many ways with new projects. In particular, I want to thank the EANO board, the Secretariat, and our PCO, the Vienna Medical Academy.

Wolfgang Grisold, MD
President of the EANO
Abstract: Paraneoplastic neurological syndromes (PNS) are rare, immune-mediated effects of a systemic cancer. PNS may affect the central and/or peripheral nervous system. Most often, the neurological symptoms precede the cancer diagnosis. The clinician must be aware of the various PNS, as early acknowledgement of such syndromes facilitates early cancer diagnosis and might improve the prognosis. Onconeural antibodies are important diagnostic markers for PNS and approximately 50% of the patients with PNS have antibodies. The PNS diagnosis is confirmed if such antibodies are present in the serum and/or spinal fluid. Supplementary investigations include MRI, EEG, and spinal fluid analysis, and these are often of diagnostic help for the diagnosis of limbic encephalitis or other paraneoplastic manifestations of the central nervous system. Neurophysiological tests are usually required to verify paraneoplastic neuropathy or neuronopathy. CT scans are used for cancer screening, but total body PDG-PET scan may be more sensitive in detecting small tumours. PDG-PET can also exhibit pathologic features in cases of limbic encephalitis, where MRI has not shown hypersignal. Other targeted investigations, such as ultrasound and various serological markers for cancer, may also be required to detect an underlying malignancy.

Key words: paraneoplastic neurological syndrome, onconeural antibody, detection

Onconeural Antibodies and Other Neuronal Antibodies

Approximately 50% of patients with PNS are seropositive for onconeural antibodies. In other words, half of the patients with PNS have no detectable antibodies and this emphasizes the point that absence of antibodies does not exclude the PNS diagnosis.

Onconeural antibodies are important diagnostic tool. The clinical manifestations of PNS often appear early in the cancer development, while the tumour is still small [9, 10], and should be performed for at least 4 years [7]. The majority of tumours are, however, detected within the first 2 years after onset of neurological symptoms. Table 1 lists an overview of the well-characterized onconeural antibodies, PNS, and their associated cancers.

The association between onconeural antibodies, cancer, and PNS is complex, as there are few antibodies specific for one type of PNS or cancer. However, in a clinical context, we often deal with a set of neurological symptoms suspected to be a PNS together with an onconeural antibody. We know that the well-characterized onconeural antibodies predict the location of the tumour more accurately than the type of PNS, and this facilitates the further investigation with regard to an underlying malignancy [8].

Table 1. Well-characterized onconeural antibodies, paraneoplastic neurological syndromes (PNS), and predominantly associated tumours.

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<td>Hu</td>
<td>PEM</td>
<td>SCLC, other</td>
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<td>Yo</td>
<td>PCD</td>
<td>Ovary, breast</td>
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<td>Ri</td>
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<td>Amphiphysin</td>
<td>PEM, stiff person syndrome</td>
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the type of antibody can give indications as to where the cancer originated [2, 8]. The cancer can then be identified at an earlier stage, specific tumour treatment can be initiated, and the chance for better neurological recovery is increased. Anti-Hu and anti-Yo are the most common antibodies in PNS in general [5, 10]. Anti-Hu is often associated with small-cell lung cancer, while anti-Yo is normally associated with ovarian and breast cancers [5, 11].

Partly characterized onconeural antibodies include anti-GluR, which are associated with paraneoplastic cerebellar degeneration and Hodgkin’s lymphoma, anti-Zic4, which are associated with paraneoplastic cerebellar degeneration and small-cell lung cancer, and anti-SOX, which are associated with Lambert-Eaton myasthenic syndrome and small-cell lung cancer [1, 12].

A number of other neuronal antibodies are sometimes associated with paraneoplastic syndromes and tumours, but less strictly and they may be present in patients with neurological syndromes, without a tumour. These include anti-NMDAR (encephalitis and teratoma), anti-AMPAR (encephalitis and various cancers), anti-VGKC complex, including anti-Lgi1 and Caspr2 (encephalitis, Morvan syndrome, neumyotonia, and small-cell lung cancer), anti-AChR (myasthenia gravis and thymoma), anti-ganglionic AChR (pandysautonomia and small-cell lung cancer), anti-GAD (stiff person syndrome, cerebellar ataxia, encephalitis, and thymoma), and anti-VGCC (Lambert-Eaton myasthenic syndrome and small-cell lung cancer [1, 12].

In the following, only PNS associated with the well-characterized onconeural antibodies will be briefly reviewed.

## Paraneoplastic Neurological Syndromes

PNS is a heterogeneous group of syndromes. To ensure a common diagnostic understanding, Graus et al [4] set up a list of criteria to define PNS in 2004. This consensus report divided PNS into definite and possible PNS based on the detection of well-characterized onconeural antibodies, neurological symptoms, and presence or absence of cancer. Syndromes that are most often associated with cancer and onconeural antibodies are defined as classical PNS. Among these are paraneoplastic encephalomyelitis, paraneoplastic limbic encephalitis, paraneoplastic cerebellar degeneration, paraneoplastic sensory neuronopathy, and paraneoplastic opsoclonus-myoclonus. Lambert-Eaton myasthenic syndrome and dermatomyositis are also classical PNS, but they are less often associated with cancer. Non-classical PNS are diseases in which the patients show diverse neurological symptoms, but well-characterized onconeural antibodies are not detected. Giometto et al reported that 18% of all patients with definite PNS had no onconeural antibodies [13].

PNS may affect all parts of the central or peripheral nervous system. Anti-Yo-mediated paraneoplastic cerebellar degeneration is characterized by loss of Purkinje cells, leading to ataxia [14]. The classical symptoms of limbic encephalitis are neuropsychiatric features, including anxiety, depression and dementia, loss of short-term memory, and seizures, which are due to medial temporal lobe affection. Paraneoplastic limbic encephalitis is associated with anti-Hu, anti-Ma, anti-CRMP5, anti-amphiphysin, and anti-Ri [1–3, 5, 15]. Paraneoplastic encephalomyelitis potentially affects most of the central nervous system, including the limbic system, cerebellum, basal ganglia, brainstem, and spinal cord, and is associated with anti-Hu, anti-CRMP5, anti-Ri, anti-Ma, and anti-amphiphysin [1–3, 5, 15]. Sensory and autonomic nerves can also be affected, either as an isolated paraneoplastic peripheral neuropathy or as part of paraneoplastic encephalomyelitis. Paraneoplastic sensory neuropathy can affect limb, trunk, and cranial nerves, the patients complain of pain, numbness, and sensory deficits. This disorder is most often associated with anti-Hu or anti-CRMP5. Paraneoplastic opsoclonus-myoclonus affects eye movement, often in conjunction with myoclonus and truncal ataxia, and is most often associated with anti-Ri, anti-Hu, anti-amphiphysin, or anti-Ma2 [1–3, 15].

### Pathogenic Mechanisms of PNS

The direct pathogenic role of onconeural antibodies has been difficult to prove. The removal of antibodies (eg, by plasmapheresis) does not cause clinical improvement in most patients with PNS. One has not succeeded to create an animal model for the classical PNS, eg, transferral of onconeural antibodies did not induce PNS in laboratory animals [12]. Several studies now indicate that PNS are T-cell-mediated and that the onconeural antibodies do not play a direct pathogenic role. However, recent laboratory research suggests that at least some of the onconeural antibodies may also induce disease. Purified IgG from patients with amphiphysin antibodies and stiff person syndrome has been injected into the subarachnoid space of rats. The rats subsequently developed symptoms similar to those seen for stiff person syndrome [16]. Furthermore, Greenlee et al have shown that rat Purkinje cells incorporate IgG, and that Yo antibodies accumulate in the cells and trigger Purkinje cell death in a non-apoptotic manner [17].

Infiltrates of mononuclear cells, neuronal degeneration, microgliosis proliferation, and gliosis are found at autopsy, for instance in paraneoplastic cerebellar degeneration [14]. Other autopsy findings are that patients with antibodies against intracellular antigens often show CD4+ and CD8+ T-cell infiltrates in the brain parenchyma [15]. Activated CD4+ T-cells have been found in the spinal fluid of patients with paraneoplastic cerebellar degeneration [18], while cytotoxic T-cells that recognize CD2R2 have been found in the blood of anti-Yo-positive patients with paraneoplastic cerebellar degeneration [19, 20]. However, the functions of the cytotoxic T-cells in PNS remain uncertain. Ma1-activated CD4+ cells have been shown to induce encephalomyelitis in mice [21]. Tani et al found that patients with small-cell lung cancer with LEMS and Hu or Yo antibodies had lower levels of a specific subtype of regulatory T-cells, the TregFoxp3+ cells, than patients with small-cell lung cancer without PNS, and concluded that low levels of Treg cells may be caused by an immune regulatory dysfunction in PNS [22]. It has also been demonstrated that epithelial ovarian cancer patients with a high CD8+/Treg ratio have an improved prognosis [23].
Some patients with cancer have onconeural antibodies, but do not develop neurological symptoms [5]. Why some patients develop PNS, while others do not, remains uncertain, but the HLA haplotype has been suggested to be important. The frequency of the HLA-DQ2+ haplotype is higher in PNS patients with anti-Hu [24], while the frequency of HLA-A2.1, HLA-A24, or HLA-B27 haplotypes is higher in patients with anti-Yo [25, 26].

Some studies suggest that tumour expression of onconeural antigens invoke the body’s tumour immunity response, but it has not been shown that this immunity response is beneficial. In a group of patients with SCLC and Hu-/VGCC antibodies, there was no association between the presence of antibodies and the prognosis of SCLC [27]. However, patients with onconeural antibodies often have smaller tumours, and spontaneous tumour regression has been noted in anecdotal cases [28, 29].

The pathogenic mechanisms in PNS lead to loss of neurons. In many cases, the neuronal damage has been so devastating that the patients have severely reduced life quality or die as a consequence of the paraneoplastic disease itself.

Clinical Work-Up

PNS Diagnosis

PNS is a differential diagnosis in most subacute and progressive neurological disorders. PNS should be suspected in all patients with rapidly progressive syndromes with inflammatory features, especially if both the central and peripheral nervous systems are affected. The diagnostic measures in suspected PNS should aim to exclude other aetiologies, to confirm that neurological symptoms are consistent with PNS, and to detect the underlying tumour.

Serological work-up, including measurement of onconeural antibodies, is important. For diagnostic purposes, serum testing of such antibodies is usually sufficient. However, onconeural antibodies can be detected at high levels in the spinal fluid in most patients with paraneoplastic CNS syndromes, indicating intrathecal antibody synthesis [30]. The spinal fluid usually shows signs of inflammation in the CSF, such as pleocytosis, increased protein concentration, a high IgG index, and oligoclonal bands in the spinal fluid [30, 31]. MRI of the central nervous system must be performed, but can be normal at onset. MRI usually shows hypersignal in the medial temporal lobes in paraneoplastic limbic encephalitis, which is often best visualized on coronal FLAIR sections. Initial MRI is obligatory in order to exclude differential diagnoses, such as metastases of the brain. EEG is usually performed in patients with encephalitis and may show generalized or localized encephalopathy or epileptic potentials. Paraneoplastic peripheral neuropathies are often asymmetrical and can be purely sensory, as part of a sensory neuronopathy, or a more classical axonal sensory-motor distal polyneuropathy. In these cases, nerve conduction and electromyography studies are important. Autonomic symptoms, in particular gastrointestinal dysmotility syndromes, are frequent in PNS associated with anti-Hu and anti-CRMP5 antibodies. Autonomic testing can be of use in such patients. However, the only paraclinical finding that is specific for PNS is the detection of onconeural antibodies. Not a single routine investigation exhibits features specific for PNS and in a given case of PNS all tests may even be normal.

Tumour Screening

If the primary cancer is unknown, cancer markers can be measured in the serum, such as NSE for lung cancer, CA-125 for ovarian cancer, AFP for immature teratomas and β-HCG/ AFP for testicular cancer [32]. If the patient smokes, the most probable underlying cancer is SCLC. Usually, a body CT scan (neck, chest, abdomen, and pelvis) is required for a malignancy screening. Ultrasound may be used to detect testicular cancer and mammography for the detection of breast cancer. A total-body PDG-PET scan is more sensitive in the detection of small tumours, particularly in the case of mediastinal lymphadenopathy. The combined modalities of whole-body CT and FDG-PET is probably the most optimal investigation. FDG-PET can also reveal hypersignal in the temporal lobes due to limbic encephalitis, where early MRI has been normal. However, FDG-PET is not an optimal modality for autoimmune encephalitis due to the high background of glucose metabolism in the brain.

If there is strong suspicion of an underlying malignancy, a new diagnostic work-up is usually needed after approximately 6 months, and may be repeated for up to 4 years [7]. In particular, all patients with neurological symptoms and onconeural antibodies should be followed closely if a cancer is not detected initially.

There are several differential diagnoses to PNS. For encephalitis, there may be several other aetiologies: herpes virus encephalitis, Hashimoto’s encephalitis, toxic-metabolic encephalopathy, Wernicke-Korsakoff’s syndrome, systemic lupus erythematosus, and other kinds of angiitis of the CNS. For cerebellar ataxias, there are also several other possibilities: toxic-metabolic cerebellar degeneration, infectious or post-infectious cerebellitis, Miller-Fisher syndrome, GAD or glia- din antibody associated cerebellar ataxia, and Creutzfeldt-Jacob disease. Patients with cancer may develop PNS-like syndromes that are due to metastases, gliomatosis, or caused by chemotherapy toxicity.

In conclusion, rapid progression of neurological symptoms where no other aetiology is found, typical constellations of neurological signs, inflammatory features in the spinal fluid, and multifocal affection of the nervous system are clinical “red flags” for PNS. The detection of onconeural antibodies should lead to a thorough screening for an underlying tumour and if the first diagnostic work-up is normal, it should be repeated in the following years.

Acknowledgements

The study was supported by grants from the Western Norway Regional Health Authority (Helse Vest).

Conflict of Interest

The authors have no conflict of interest.
Paraneoplastic Neurological Syndromes

References:
Neurologic Complications in Multiple Myeloma and Plasmacytoma

Roser Velasco, Jordi Bruna

Abstract: Neurologic complications in plasma cell malignancies are frequently seen in the practice of neuro-oncology, involving areas such as the peripheral and central nervous system. These can be the first symptoms, leading to the diagnosis of the underlying disease, or they may appear during the course of the illness. Radicular pain secondary to compressive radiculopathy is the most common neurologic complaint. Additionally, neurotoxic side-effects derived from the first-line drugs employed are frequently observed during treatment of the malignancy, particularly sensory distal polyneuropathies. Multiple myeloma (MM) is the most common malignant plasma cell disorder, accounting for approximately 10 % of all haematological malignancies. A wide spectrum of neurological complications has been described associated with MM, ranging from carpal tunnel syndrome to the life-threatening spinal cord compression. Plasmacytoma is defined as a localized proliferation of malignant plasma cells, and it may eventually turn into MM. Plasmacytoma may occur inside or outside the bone marrow, with neurologic involvement depending on the placement of the mass. The POEMS syndrome is a paraneoplastic disorder associated with the presence of a bone plasmacytoma. Peripheral neuropathy is always present in the POEMS syndrome. Moreover, clinical manifestations secondary to central nervous system involvement are being increasingly recognized, like papilloedema, stroke, and pachymeningitis. This review will focus on the neurologic complications associated with MM, plasmacytoma, POEMS syndrome, and their management. Furthermore, neurologic complications derived from treatment will also be reviewed, especially the treatment of emergent peripheral neuropathy.

Key words: multiple myeloma, plasmacytoma, POEMS, neurological complications, neuropathy, neurotoxicity

Introduction

Malignant plasma cell dyscrasias are characterized by neoplastic proliferation of a single clone of plasma cells, typically producing a monoclonal immunoglobulin called paraprotein. Among them, plasmacytoma and multiple myeloma (MM) represent a spectrum and probably the natural progression of the same illness. Plasmacytoma is defined by the presence of a localized plasma cell tumour without evidence of neoplastic plasma cells in bone marrow (< 5 %) and absence of other features of myeloma. Plasmacytoma most frequently occurs in bone (plasmacytoma of bone), but can also be found outside bone in soft tissues (extramedullary plasmacytoma). Both can present as solitary or multiple lesions, the latter more predictive of progression to myeloma. The POEMS syndrome is a paraneoplastic disorder associated with the presence of a bone plasmacytoma and considered the same entity as osteosclerotic myeloma [1, 2].

Multiple myeloma (MM) is the most frequent malignant plasma cell disorder, accounting for approximately 10 % of all haematological malignancies. MM is defined by the presence of paraprotein in the serum and/or urine (serum > 3 gr/dl), at least 10 % neoplastic plasma cells in the bone marrow or their presence in other tissue, and evidence of end-organ damage, related to the underlying plasma cell disorder, including hypercalcaemia (C), renal failure (R), anaemia (A), and bone lesions (B), commonly named CRAB symptoms acronymically. Smoldering or asymptomatic MM is present when monoclonal protein > 3 gr/dl or infiltration at the bone marrow (> 10 %) is not accompanied by CRAB symptoms [1, 3].

Neurologic complications are frequent during plasmacytoma and myeloma, and constitute the most frequent non-CRAB-presenting symptom in MM [4, 5]. Patients can present with almost the whole spectrum of neurologic complaints, affecting areas such as peripheral and central nervous system (Table 1). In this article, discussion focuses on neurologic complications associated with plasmacytoma and multiple myeloma, and the therapies employed in their management.

Direct Complications of Myeloma and Plasmacytoma

Spinal Complications

The most common neurologic complaint in these patients is radicular pain, sometimes with associated weakness and numbness, due to nerve-root compression by direct extension of vertebral plasmacytoma or, more frequently, a pathological vertebral fracture with secondary foraminal stenosis [5]. In this setting, the diagnostic approach is magnetic resonance imaging (MRI) or computed tomography (CT) and electromyography when needed. The most frequent local neurologic complication involving the central nervous system (CNS) is spinal cord compression, which can be related with a bone fragment retrodistalised from a vertebral fracture or extension of plasmacytoma arising from bone marrow of the vertebral body and extending to the anterior epidural area. Although incidence has decreased in recent years, partially because of extensive use of bisphosphonates, it still occurs in approximately 5 % of patients with MM [5] and in 3 % as the presenting symptom [4]. The thoracic spinal cord is the most frequent level involved [6].

Clinical features include back pain, which can be associated with radicular pain and motor, sensory, and sphincter impairments to some degree, which can usually be mild and mani-
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 fest abruptly when spinal cord compression occurs, making early diagnosis difficult and requiring great awareness by the clinician. Back pain, mainly when recumbent in patients with myeloma, should arouse suspicion of this complication, with mandatory spine MR. When a soft tissue mass is compromising the nerve-root, radiotherapy or even surgical resection may be indicated, with analgesic and decompressive intention. The therapy of choice for spinal cord compression in these patients is radiotherapy, with long-course schedules of at least 30 Gy in 10 sessions [7] in addition to corticosteroids. The role of decompressive laminectomy before radiotherapy is controversial. Current evidence does not support the use of surgical decompression, due to the similar outcome achieved with radiotherapy alone compared to surgery plus radiotherapy [8, 9]. No specific therapy is usually indicated in nerve-root compression without soft tissue mass, and management of pain with medical treatment is the best approach [5].

Percutaneous vertebroplasty is a minimally invasive procedure involving the injection of bone cement within a collapsed vertebral body, which is increasingly indicated in related MM pathological spinal fractures that cause pain unresponsive to conservative treatment. This technique has analgesic and stabilizing effects on the spine, with demonstrated effectiveness [10]. Its major technical drawbacks are the potential for neural compromise and pulmonary embolism of cement into epidural space and perivertebral veins. Percutaneous vertebroplasty is primarily contraindicated if neurological compromise or epidural component is present, owing to the high risk of exacerbating neurological symptoms, although recently published studies show positive evidence of the safety of the procedure in these patients [11].

Cranial Complications

Patterns of intracranial MM include (1) osteo-dural MM or plasmacytoma (cranial MM) and (2) brain parenchyma plasmacytoma [12].

Osteo-dural plasmacytoma is the most frequent form of cranial plasma-cell neoplasm, usually arising from osseous lesions in the cranial vault, skull base, nose, or paranasal sinuses. Clinical presentation includes pain, headache, seizure, or cranial palsies (Figure 1). The isolated primary dural plasmacytoma is very rare because dural deposits usually result from contiguous bone lesions. Radiological findings of cranial plasmacytomas are not specific and usually mimic other neoplastic lesions, with pathology needed to establish the definitive diagnosis. CT scan and MRI show well-defined destructive masses arising from osseous structures, or dural-based mass that may appear iso- to hyperdense on CT scan, T1-weighted images iso- to high signal intensity, and T2-weighted images with a hypointense signal on MRI, with variable contrast enhancement [13]. Recently, PET-CT was shown to detect extramedullar plasmacytomas also in the CNS [14]. Among cranial plasmacytomas without MM at diagnosis, cranial base location seems to carry an increased risk of progression to MM compared to dural-based lesions [15].

Treatment of cranial plasmacytoma includes surgical resection with adjuvant focal radiotherapy [16]. When multiple plasmacytoma or MM is present, additional systemic chemotherapy or even a transplant should be considered. Recently, cranial responses to new agents (bortezomib, thalidomide, lenalidomide) have been reported [12]. Much rarer is the presence of an intraparenchymal brain plasmacytoma without evidence of extension from osseous or dura, which can be manifested as brain haemorrhage [17].

Prognosis of MM patients with osteodural plasmacytomas is worse than in MM patients without cranial involvement, with reported median overall survival of 25 and 46 months, respectively [12].

Leptomeningeal Myeloma

Leptomeningeal myeloma (LMM) has an estimated incidence of 1 % of MM patients [18, 19] and is defined as the detection of malignant monoclonal plasma cells in the cerebrospinal fluid in the presence of suggestive symptoms. The most common presenting features include radiculopathy, cauda equina syndrome, encephalopathy, and cranial palsies [18–20]. LMM requires a high index of suspicion, mainly when radicular pain is the clinical presentation. LMM seeding is usually concomitant with aggressive MM rather than a sign of progression to a more advanced disease, and is usually diagnosed at younger ages (54–62 years) and after a median of 13–17 months after MM diagnosis. Inherent biological features of the disease have been suggested by several authors as primarily responsible for predisposition to LMM and conferring a higher risk of CNS relapse: high myeloma burden, increased LDH levels, other extramedullary manifestations, IgD paraprotein, lambda subtype, plasma cell leukaemia, plasmablastic morphology, high-risk chromosomal abnormalities, and absence of CD56 in myeloma cells [21]. LMM confers a very poor prognosis and is usually a terminal event. LMM has a median survival of 2 months, increasing up to 4 months in a series treated intensively with radiotherapy as well as systemic and intrathecal chemotherapies [12, 18, 20].

![Table 1. Neurological complications associated with MM and plasmacytoma](image-url)
Remote Complications of Myeloma and Plasmacytoma

Peripheral Nervous System

Peripheral neuropathy (PN) is a frequent remote manifestation of malignant plasma cell neoplasms. It can be found in the setting of classical MM or be associated with plasmacytoma of the bone, as part of the POEMS syndrome. This acronym designates osteosclerotic myeloma with polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal protein (M), and skin changes (S). However, not all features in the acronym are present in all POEMS patients, and, conversely, the acronym does not include several of the characteristic features of the syndrome. In 2007, new diagnostic criteria were established, which require the presence of polyneuropathy and monoclonal gammapathy in addition to one of the 3 major criteria (sclerotic bone lesion, Castleman’s disease, and vascular endothelial growth factor elevation) and one of the 6 minor criteria (organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilloedema, and thrombocytosis/polycythaemia) [22].

Several characteristics allow to distinguish between MM and POEMS neuropathy. In MM, PN is present at diagnosis in approximately 12% of patients, and up to 50–62% of MM patients present with subclinical neuropathy when exhaustive neurologic examination and nerve conduction studies are performed [23]. MM-related PN is thought to be related to toxic phenomena, or perineural or perivascular paraprotein deposition. PN in MM usually manifests as length-dependent axonal polyneuropathy, mild in intensity, and affecting more sensory than motor fibres. However, amyloid components can also be present in up to 6% of patients with MM. In these patients, neuropathy is more frequent, reaching incidences of 30–40%. Burning pain, autonomic features like orthostatic hypotension, gastric disturbances, and impotence are the main characteristics, secondary to the predominately small-fibre involvement [24].

In POEMS, neuropathy is always present, as one of the 2 major criteria necessary for the diagnosis. Frequently, PN is the first complaint and the guide symptom that leads to diagnosis. The characteristics of neuropathy are similar to those of chronic inflammatory demyelinating polyneuropathy (CIDP), and patients may be misdiagnosed with idiopathic CIDP or monoclonal gammapathy of undetermined significance-associated neuropathy. Furthermore, acute presentations of POEMS-associated neuropathy have been described as mimicking the Guillain-Barré syndrome [25]. Clinically, they are indistinguishable, although POEMS neuropathy seems more
frequently associated with leg pain, muscle atrophy, and distal muscle weakness than classic CIDP [26]. Cerebrospinal examination usually shows albuminocytological dissociation, similar to CIDP and the Guillain-Barré syndrome. Electrodiagnostic tests reveal a demyelinating neuropathy, predominantly in the legs, with distal motor involvement. Compared with idiopathic CIDP, POEMS nerve conduction studies show a more uniform slowing, lack of temporal dispersion or conduction blocks on nerve conduction studies with less prolonged distal motor latency, a higher terminal latency index in the median nerves, and unrecordable tibial and sural responses, suggesting demyelination predominant in the nerve trunk rather than in the distal nerve terminals, and axonal loss in the lower limb nerves [27–29]. Interestingly, detection of this clinical and neurophysiologic pattern can be useful before development of typical systemic manifestations, to be aware of the possibility of POEMS. Regarding the pathologic mechanism, polynuropathy in the POEMS syndrome is thought to be a direct or indirect effect of angiogenic factors on endoneurial nerve vessels, producing a degree of endoneurial oedema [29, 30]. With regard to treatment, no intervention reverses neuropathy associated with MM, and treating myeloma can cause or exacerbate existing PN. Neuropathy associated with the POEMS syndrome usually improves with plasmacytoma treatment. In contrast to CIDP, plasmapheresis and intravenous immunoglobulin have no clinical benefit. Improvement usually begins within the first 3–6 months after treatment, although delayed recovery is not known and can take up to 2 years [22].

Finally, another frequent neurological complaint in multiple myeloma patients is compressive neuropathies secondary to amyloid deposits, such as the carpal tunnel syndrome [5, 31]. Typically, median nerve compression at the wrist is bilateral and not predominant in the dominant hand. Rarely, amyloid can also be detected in muscles, causing weakness, muscle stiffness, pseudohypertrophy, and myalgias [32].

Cerebrovascular Complications
Stroke and venous thrombosis have been classically described with MM, related with the hyperviscosity syndrome and thrombophilia. Hyperviscosity is estimated to occur in 2–6 % of MM, depending on the type of heavy chain involved (IgM > 3 g/dl [very rare in MM], IgG > 4 g/dl, IgA > 6 g/dl). Strokes usually involve small vessels, frequently causing encephalopathy more than focal deficits, in addition to headache, visual disturbances, and mucocutaneous bleeding. Treatment requires urgent plasmapheresis [33]. Further, increased hypercoagulability and thrombophilia are recognized features associated with MM. At least 4 mechanisms of hypercoagulability specifically related to MM have been suggested:
1. impairment of the fibrinolytic pathway due to the inhibition of fibrin structure by an abnormal amount of immunoglobulins
2. abnormal antibodies acting as an autoantibody against natural anticoagulants
3. procoagulant activity caused by the pro-inflammatory status associated with myeloma
4. resistance to activated protein C by non-factor V Leiden [34, 35].

Importantly, reports of MM patients treated with thalidomide and lenalidomide suffering from stroke or cerebral vein thrombosis [36] remind us of the increased prothrombotic risk of these drugs in MM.

In addition, cerebrovascular events have also been related with POEMS [37, 38]. In a retrospective study at the Mayo Clinic, nearly 10 % of all POEMS patients developed stroke after POEMS diagnosis. Interestingly, there was no difference between POEMS patients with and without stroke in regard to common cardiovascular risk factors. Only a high platelet count and the presence of plasma cells in the bone marrow at POEMS diagnosis were predictive of a higher stroke risk. In this series, patients with thrombocytosis > 500,000 carried a risk of cerebral infarction of 29 % at 5 years. Noteworthy, none of the events occurred after successful treatment of the underlying syndrome; hence, the importance of treating the underlying disease to minimize the risk of stroke [39].

Other POEMS-Related Central Nervous System Complications
Papilloedema is a characteristic finding in 30–64 % of patients, which can be asymptomatic and usually bilateral. It is associated with intracranial hypertension, inflammation, or an increase of vascular permeability [40, 41]. Related symptoms are headache, transient vision obscuration, enlarged blind spots, and progressive constriction of the visual field. Blurred vision is reported by 45 % of patients when directly questioned [40], and rarely constitutes the first manifestation [42]. In case of symptomatic papilloedema, some authors suggest performing an intracranial pressure study and treatment with acetazolamide if there is evidence of intracranial hypertension [41].

Recently, Briani et al described pachymeningeal involvement in 9 out of 11 patients with POEMS. Pachymeningitis was asymptomatic, and findings on MRI showed meningeal thickening and enhancement, more evident in the falx cerebri and the medial portion of the cerebellar tentorium. Pathological studies in 2 patients showed absence of inflammatory changes, increased vessel density and thickness, over-expression of VEGF and VEGFR2 on arterial smooth muscle and meningotheelial cells, and proliferation of meningotheelial cells. Histology findings were distinct from pachymeningeal specimens of other aetiologies. The authors point out that pachymeningeal involvement may be part of the POEMS spectrum and could have been overlooked [43].
in the differential diagnosis, owing to the immunosuppressive nature of these diseases.

**Treatment-Related Neurologic Complications**

Neurological impairment in these patients can be due to the therapy with cytostatic drugs (vincristine, high-dose melphalan), immunomodulatory drugs such as thalidomide or corticosteroids, and bortezomib. Neurological complications associated with stem cell transplantation are beyond the scope of this review.

PN is the main non-haematological dose-limiting side effect of bortezomib, thalidomide, and vincristine, which may impair the quality of life of MM patients [45–49]. Table 2 summarizes the main features of these induced peripheral neuropathies. Identification of risk factors associated with the development of drug-induced neuropathy is a matter of research to optimize the safety management of these patients, with conflicting results with regard to age, pre-existing neuropathies, or diabetes mellitus. Only dosage is an involved factor in all cases. Meanwhile, close neurological monitoring of patient candidates for these therapies seems the best way to minimize the risk of severe and disabling neuropathies, advising the treating physician in the application of dose modification guidelines, without negative impact in MM response [51, 52]. NCS should be performed at baseline to detect subclinical PN and during follow-up it can help to discriminate peripheral neuropathy from other complications like radiculopathy.

Varicella-zoster virus reactivation is a common and serious adverse event related to bortezomib treatment, with an incidence rate of 10–60% and a higher risk of post-herpetic neuralgia [53]. Therefore, prophylactic use of acyclovir is advocated in these patients, although the potential renal and neurological toxicity related with long-term acyclovir treatment should be borne in mind [54].

Steroid myopathy is frequently seen in high-dose dexamethasone schedules, as with the classical VAD protocol (vincristine, adriamycin, and dexamethasone), with an 8-% incidence described [55]. Diagnosis is mostly clinical, with predominant psoas and quadriceps involvement; muscle enzymes are rarely increased, and electrophysiological analyses demonstrate unspecific and variable abnormalities. Muscle biopsy should remain exceptional, since there are no specific anatomicopathological findings. Treatment is based on reduction or, if possible, discontinuation of the steroid or replacement by

<table>
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<tr>
<th>Table 2. Characteristics of neuropathy induced by agents used in the treatment of MM [45–50].</th>
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<tr>
<td><strong>Bortezomib</strong></td>
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<tr>
<td>Incidence¹</td>
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<tr>
<td>9–19% ≥ grade 3</td>
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<tr>
<td>Time of onset</td>
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<tr>
<td>8% PN &gt; 2 after one cycle</td>
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<tr>
<td>Related with cumulated dose</td>
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<td>Plateau in risk at &gt; 30 mg/m²</td>
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<td>Neuropathy features</td>
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<td>Autonomic involvement</td>
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<td>Coasting effect²</td>
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<td>Nerve conduction studies</td>
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<td>Mechanism of neurotoxicity</td>
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<td>Risk factors</td>
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<td>Prior vincristine treatment</td>
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<tr>
<td>MM recurrent</td>
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<td>Twice-weekly schedules</td>
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<td>RDM1, CASP9, ALOX12, LSM1</td>
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<td>(associated with early PN)</td>
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<tr>
<td>ERCC3, ERCC4, IFNGR2, MRE11 (PN at cycles 2–3)</td>
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<tr>
<td>CTLA4, CTSS, GJE1, PSMB1, TCF4, and DYNC1</td>
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<tr>
<td>Special considerations</td>
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<td>Fulminant neuropathies described with underlying Charcot-Marie-Tooth neuropathy</td>
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PN: Peripheral neuropathy; ¹ Grade of neuropathy according to NCI.CTCv (2 or 3); ² coasting effect is described as worsening of the neuropathy the first months after stopping the treatment.
non-fluorinated glucocorticoids, such as prednisone. Importantly, it can often affect respiratory function even when proximal limb muscles remain strong [56]. Finally, encephalopathy and seizures in MM patients, apart from the metabolic disturbances detailed above, can also be associated with treatment with high-dose melphalan, commonly used as an induction to stem cell transplantation; reversible posterior leukoencephalopathy syndrome induced by bortezomib has rarely been reported [57].

Concluding Remarks

- Neurological complications associated with multiple myeloma and plasmacytoma are commonly observed in clinical daily practice. Early diagnosis and intervention in the most frequent complications can prevent disabling outcomes in many cases.
- Neurological complaints can involve the peripheral and central nervous system, secondary to direct or remote effects of the plasma cell neoplasm.
- The spectrum of complications associated with the POEMS syndrome has grown in recent years to include meningal thickness and an increased relative risk of stroke.
- Nerve conduction studies are useful in distinguishing neuropathy associated with MM and POEMS, and can also be helpful in early differentiation between chronic immune demyelinating neuropathy and POEMS-related polyneuropathy.
- The high rate of peripheral neurotoxicity induced by first-line therapies used against MM and POEMS syndrome makes neurological monitoring advisable in order to minimize the risk of severe and disabling neuropathies.

Acknowledgments

The authors thank Dr C Majós for his contribution. In reminiscence of Dr J Petit.

Conflict of Interest

RV has no conflict of interest to disclose.

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Neurologic Complications in Multiple Myeloma and Plasmacytoma
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Introduction: General Concepts

Hematopoietic stem cell transplantation (HSCT) is a complex procedure that in recent years has been increasingly used for a number of haematological and non-haematological diseases [1]. An international consortium estimated an annual worldwide number of approximately 60,000 procedures for 2009 (http://www.ibtmr.org).

In decreasing order of frequency, haematologic indications are: multiple myeloma, non-Hodgkin lymphoma, acute myeloid leukaemia, Hodgkin’s disease, acute lymphoblastic leukaemia, myelodysplastic syndrome, aplastic anaemia, and other leukaemias. While mainly used for haematological malignancies, HSCT is also being used for solid tumours, such as breast cancer, and severe autoimmune diseases, including multiple sclerosis [2].

HSCT always includes several crucial steps (Figure 1), as dictated by the scientific principles underlying this therapy. The first step is to eliminate the patient’s abnormal hematopoietic system. In order to do this, ablative chemotherapy regimes sometimes potentiated with total body irradiation are used (“conditioning regime”). This is the rationale for using HSCT in the treatment of haematological malignancies, other haematologic disorders, such as aplastic anaemia, and autoimmune diseases. In the case of non-haematological malignancies, the objective is to use aggressive chemotherapy against the tumour and myeloablation is an unwanted “adverse event”, which requires HSCT for rescue. The second step is to reconstitute a functioning hematopoietic system. This process starts with the infusion of hematopoietic stem cells (“the graft”).

Hematopoietic stem cells have an extremely high regenerative capacity. It has been shown in animal experiments that it is possible to regenerate the whole hematopoietic system of a recipient after transplantation of a single hematopoietic stem cell. Also, hematopoietic stem cells can be cryopreserved, allowing for donor and recipient to be temporally and geographically distant.

Depending on the source of “the graft” the transplant is classified as either autologous or autogenic, when the source is the patient himself, allogeneic transplant, when the source is a donor, be it related or unrelated, or syngeneic, in the rare event that the donor is a genetically identical twin. Allogeneic and autologous transplants differ in terms of outcome, frequency and type of complications. Allogeneic transplants are usually very effective in controlling the original disease but are associated with a high mortality rate (up to 40%). Mortality is much lower in autologous transplants (< 10%) but at the expense of a higher risk of relapse of the original disease. Both medical and neurological complications are more frequent in allogeneic transplants [3]. The most dreaded of these complications is the “graft-versus-host disease” (GVHD; for an example see Figure 2), which is difficult to treat and may be fatal. Here, immune cells developing from the donor’s hematopoietic system react against host antigens, which they recognize as “foreign”. In order to minimize the risk of this complication antigenic similarity between donor and recipient should be striven for by carefully matching them for the Human Leukocyte Antigen (HLA) system. Preferably, donor and recipient should be related and the closer their familial relation is, the less frequent and severe the GVHD will be. Also, potent immunosuppressive drugs are used to prevent GVHD, further increasing the risk of complications in allogeneic transplantation, either in the form of adverse medical reactions or through favouring opportunistic infections and secondary neoplasms.

It should be noted that, in some circumstances, the immunological reaction of the graft against host antigens might be beneficial when the target antigen is present in the malignant cell. This is known as the “graft-versus-leukemia/tumour effect” and it is the rationale for “minitransplant” protocols. In these, less aggressive ablative regimes can be used with improved tolerance. The result is the co-existence of 2 different hematopoietic systems in the host, a situation known as chimerism, namely the host’s original hematopoietic system, which will include some malignant cells, and the donor’s hematopoietic system. It is expected that the immune system developing from the donor will eventually eliminate any residual malignant cells. Because the ablative regimes are less
toxic in minitransplants, this procedure is suitable for elderly patients or those with poor pre-transplant general medical condition, be it from co-morbidities or from the disease. Medical and neurological complications are nevertheless frequent, given that patients are usually less fit [4].

Overall, neurological complications after HSCT are frequent, with estimates ranging from 8–42% in the different series, depending on how strict the inclusion criteria are [5–14].

When seeing a patient with a suspected neurological complication from HSCT, it must be kept in mind that they have undergone a long and complicated process, including the use of several highly toxic drugs posing high demands on different metabolic systems. Thus, a thorough revision of medical records from the beginning of the haematological disease should be done to get a wider point of view. Particular attention should be paid to the following key points:

– Previously used treatments, including those for the haematological disease, but also the ones used for possible complications, such as infections. Pre-existing damage, due to toxicity from previous treatments, may be aggravated by the conditioning regimes used for HSCT.

– The moment of presentation of the complication in relation to the chronology of the transplant. This information can be very useful for narrowing down the differential diagnosis.

– Co-existent non-neurological complications and co-morbidities. On the one hand, these can have an impact or predispose to certain complications. For example, renal failure can predispose to posterior reversible encephalopathy syndrome in patients taking cyclosporine. On the other hand, systemic complications may help orienting the differential diagnosis. This is particularly relevant for infections, as a co-existent local infection may spread to the CNS. For example, in a patient with focal neurological symptoms and disseminated cortico-subcortical micro-abscesses, knowing that they are also being treated for pulmonary aspergillosis would suggest haematogenous spread.

Also, physicians dealing with these patients should become familiar with certain facts and general principles regarding HSCT, including:

– Neurological complications more commonly associated with the original disease. For example, one study suggested that patients with myeloblastic leukaemia have a higher risk of CNS subdural bleeding.

– Neurological complications more commonly associated with the drugs used.

– Atypical clinical and radiological presentations of neurological conditions, which are often seen in these patients. For example, cerebral toxoplasmosis may not present with the typical focal lesions surrounded by a contrast-enhancing ring, but rather with toxoplasmic encephalitis or lesions with a haemorrhagic component.

– The chronology and stages of the HSCT and the most common complications occurring at each stage. This is particularly relevant for infections. At each stage of the transplant different forms of immune response may be affected, resulting in a different propensity to infection from certain microorganisms. For example, bacterial infections are more common during the initial periods after myeloablution, due to neutropenia, whereas viral infections are more common later on, while cell-mediated immunity is still inefficient.

In the following section, we will discuss the different stages of the HSCT and the most common neurological complications seen at each of them.

### Stages of the Transplant Procedure and Associated Neurological Complications

#### Pre-Transplantation Period

**Stem Cell Harvesting**

Hematopoietic stem cells may be harvested from different sources, including bone marrow, umbilical cord blood, and peripheral blood. The traditional source of hematopoietic stem cells is bone marrow, aspirated from posterior or anterior iliac crests. Complications of this procedure include local
haemorrhage, which may compress local nerves, such as the sciatic nerve, and accidental puncture of the subarachnoid space, which may cause intracranial hypotension [15].

Hematopoietic progenitors can also be recovered from peripheral blood, a method commonly used for autologous transplantation. In order to mobilize enough stem cells from the bone marrow to the peripheral blood, recombinant hematopoietic growth factors that reduce adhesion of stem cells are administered to the patient/donor (ie, Granulocyte-Colony Stimulating Factor [G-CSF], Granulocyte-Macrophage-CSF [GM-CSF]). Because these drugs are also cytokines they may induce hypercoagulability or exacerbate autoimmune disease. The progenitors are later collected through apheresis.

Myeloablation
Myeloablative conditioning regimes include high-dose chemotherapy, which can be combined with total body irradiation. This is more commonly done in allogeneic transplantation. Different chemotherapeutic agents can be used, depending on the original disease and the source of the graft. Many of these highly toxic drugs can potentially cause neurological complications. For example, ifosfamide and busulfan may cause encephalopathy, myoclonus, and seizures. Patients receiving treatment with busulfan are treated preemptively with antiepileptic drugs for this reason. Other commonly used chemotherapeutic agents which can be neurotoxic include cytarabine (cerebellar ataxia, peripheral neuropathy) and methotrexate (myeloradiculopathy).

Patients receiving allogeneic transplants will also be treated with immunosuppressant drugs, intended to reduce the risk of GVHD, further contributing to neurologic toxicity.

Pre-Engraftment Period
Day 0: Stem Cell Infusion
After myeloablation is completed, stem cells are infused intravenously to reconstitute the hematopoietic system. The day of infusion is customarily defined as “day 0”. Infusion of stem cells is a relatively simple procedure and complications are rare. Occasionally reported neurological problems include stroke and transient global amnesia. Dimethylsulfoxide, a chemical used for cryopreservation of hematopoietic stem cells, has been linked to rare cases of encephalopathy, seizures, and posterior reversible encephalopathy syndrome [16, 17].

Days 0–30: Bone Marrow Aplasia
As a consequence of myeloablation patients are left in a state of aplasia that will persist until the transplant engrafts in the bone marrow of the recipient. This process usually takes 2 weeks after stem cell infusion. Time to engraftment is usually longer in allogeneic transplantation and when stem cells are obtained from bone marrow. Any delay or failure of the transplant to engraft prolongs the period of pancytopenia, during which serious medical and neurological complications may ensue. Commonly described medical complications in this period are mucositis, hepatic venoocclusive disease, and interstitial
neurologic complications of Hematopoietic Stem Cell Transplantation

Drug toxicity from immunosuppressive drugs used to prevent GVHD is also a common cause of neurologic symptoms. These regimes frequently include steroids and calcineurin inhibitors, such as cyclosporine or tacrolimus. Steroids may cause psychiatric symptoms, anxiety, insomnia, memory problems, myopathy, and epidural lipomatosis. Cyclosporine and tacrolimus frequently induce tremor, paraesthesias, and seizures. Isolated seizures may not require discontinuation of the drug, especially if these occur with toxic blood levels. Dose reduction may resolve the problem. Rarely, calcineurin inhibitors may induce posterior reversible encephalopathy syndrome (PRES), a very characteristic clinical and radiological entity [18]. Common clinical symptoms include headache, altered level of consciousness, seizures, and visual cortical dysfunction. Brain MRI typically shows bilateral hyperintense lesions in T2-weighted sequences involving the white matter of the posterior areas of the brain. It should be noted, however, that the cortex and more anterior areas of the brain may also be involved and that unilateral changes are also possible. Cortical enhancement has also been occasionally described. FLAIR sequences are more sensitive for detecting alterations. These lesions are thought to represent vasogenic oedema. It is important to recognize and treat other factors that may contribute to this syndrome: renal failure, sustained arterial hypertension, hypomagnesaemia, hyponatraemia, and simultaneous use of other drugs, such as chemotherapeutic agents (cyclophosphamide) and antibiotics (linezolid). Although PRES resolves without complications in most cases, if treated promptly, it must be emphasized that delay or inadequate treatment may result in permanent damage, related to brain haemorrhage, especially if thrombocytopenia co-exists, or atrophy of the involved cerebral areas. Unlike with isolated seizures, the offending drug should be discontinued. The occurrence of PRES seems to be of prognostic value. One study found that patients who developed this complication within the first 100 days after HSCT had a shorter survival time [7].

Developing neurologic complications with one calcineurin inhibitor does not necessarily imply that another will cause the same problem and, therefore, when neurologic complications occur with cyclosporine or tacrolimus, it is a reasonable first step to attempt switching to the alternative drug.

To summarize, the most frequent symptom leading to the consultation of a neurologist at this stage is acute diffuse encephalopathy with or without seizures. A careful clinical evaluation should be followed by brain neuroimaging (CT or preferably MRI) and lumbar puncture should be considered if CNS infection is suspected. Neuroimaging may disclose brain haemorrhage or PRES. If imaging is normal, the differential diagnosis includes organ failure, sepsis, or drug toxicity. Among the different drugs commonly used at this stage, cyclosporine is the most frequent offender. Other possibilities include steroids, amphotericin, acyclovir, and opioid drugs. Two treatable conditions in this setting that should not be missed are Wernicke encephalopathy and non-convulsive status epilepticus. Very often the aetiology will be multifactorial. Many episodes of post-transplant delirium may be transient and benign, but some patients may develop chronic cognitive deficits.

Post-Engraftment Period

Days 30–100: Engraftment

Once the hematopoietic stem cells have engrafted, the 2 main medical complications that may occur are infections and GVHD [19, 20].

At this stage, neutropenia has resolved and the external barriers should be healed, but the developing new immune system is still immature, and cell-mediated immunity, humoral immunity, and phagocytic function are not yet effective. For example, the engrafted immune system cannot mount an adequate immune response against polysaccharide-encapsulated bacteria, such as pneumococcus, haemophylus influenza, or meningococcus. Vaccination against these germs is thus recommended. Also, in allogeneic transplantation, the need for immunosuppressants to prevent GVHD will increase further the risk of infections.
Neurologic Complications of Hematopoietic Stem Cell Transplantation

For this reason, it is common practice to use prophylactic antimicrobial drugs. The choice of these drugs must be individualized for each patient. Immune status, for example, presence of antibodies against HSV, and history of previous infections, for example tuberculosis, are important considerations in this regard and should be carefully assessed before transplantation. Commonly used drugs include wide-spectrum antibiotics, fluconazol (Candida spp), acyclovir (Herpes virus), and co-trimoxazole (Pneumocystis spp). When dealing with a patient with a suspected infection, it is crucial to know their exact prophyactic regime, as this may alter the possible causative germs.

Bacterial infections at this stage are less frequent than in the pre-engraftment period. They are commonly caused by opportunistic bacteriae, such as Listeria spp, which may cause meningitis or rombonecephalitis (encephalitis involving brainstem and cerebellum), and filamentous bacteria, such as No-cardia spp.

Viral infections are more common at this stage, owing to the inefficient cellular and humoral immune response. This can lead to reactivation of latent viruses in seropositive patients or in the stem cells from the donor. Amongst these cytomegalovirus (CMV) infections are common and may involve the CNS, often with fatal consequences. Adenoviral infections are also frequent and may disseminate and cause meningonecephalitis [21]. Limbic encephalitis resulting from reactivation of Human-Herpes-virus type 6 (HHV6) is a characteristic infectious complication of patients with allogeneic HSCT at this stage [22]. Patients present with confusion, seizures, and anterograde amnesia. Brain MRI typically shows signal changes in the mesial temporal lobes. Again, FLAIR sequences are more sensitive. EEG may show epileptic discharges arising from the temporal lobe. CSF may show pleocytosis or raised protein, but it can be normal. CSF PCR for HHV6 confirms the diagnosis. Treatment with foscarnet may be effective, but cognitive sequelae are common.

A common fungal infection in this period is pulmonary aspergillosis, which may seed haematogenously to the CNS. Brain MRI may show multiple small cortico-subcortical abscesses. These fungi have a particular predilection for blood vessels, and the lesions may be associated with areas of ischemia or haemorrhage [23]. Others include Cryptococcus spp and Candida spp. The clinical syndrome can be helpful in establishing the aetiology of fungal infections. Filamentous fungi tend to cause brain abscesses (Aspergillus) whereas yeast fungi tend to cause meningitis (Cryptococcus spp, Candida spp).

Also arising at this stage, and from here onwards, 2 specific complications may occur, related to the development of a more effective cell-mediated and humoral immunity: immune reconstitution inflammatory syndrome (IRIS), also known as immune recovery syndrome, and GVHD. In IRIS, as the immune system matures and cell-mediated immunity recovers, an exaggerated inflammatory response against previously acquired infections may develop, which can either, paradoxically, worsen previous symptoms (paradoxical IRIS) or uncover a previously asymptomatic opportunistic infection (unmasking IRIS) [24]. The optimal treatment for this condition is not well-established. In paradoxical IRIS, reactions causing spontaneous improvement are frequent and additional therapy is seldom needed. In unmasking IRIS, the most common approach is to administer antimicrobial drugs against the causative agent. In severe cases, immune-modulator agents, such as corticosteroids or non-steroidal anti-inflammatory drugs can be used to suppress inflammation until the infection has been controlled. CNS infections which are commonly associated with IRIS include viral encephalitis (CMV, Varicella-Zoster virus [VZV]), fungal CNS infections (Cryptococcus spp, Aspergillus spp, Candida spp), and progressive multifocal leukoencephalopathy (JC virus).

In GVHD, graft-derived allogeneic T-cells react against antigenic targets of the host cells, which they recognize as foreign. The incidence is higher in recipients of mismatched (non-identical HLA) or matched unrelated donors, in older patients, and in patients who have not received adequate immunosuppressive regimes [25]. There are 2 well-characterized clinical forms: acute and chronic GVHD. Acute GVHD develops within the first 100 days after transplantation and is a specific syndrome involving skin, liver, and the gastrointestinal system. It presents most commonly 4 weeks after transplantation with a pruritic erythematous rash. The liver is also often involved causing cholestasis, with raised levels of bilirubin, alanine amino-transferase (ALT), aspartate amino-transferase (AST), and alkaline phosphatase (AP). Intestinal involvement will manifest as diarrhoea and abdominal pain. Acute GVHD very rarely affects the nervous system and neurological complications are more often related to the treatments used for prevention and management of the condition: high doses of intravenous corticosteroids, antithymocyte globulin, and monoclonal antibodies targeting T-cells.

Late Post-Transplantation Period

Days > 100: Chronic Phase
Neurological complications arising at the chronic stage include infections, chronic GVHD, and secondary neoplasms.

The most common infections are again viral. VZV is the most frequent causative agent. This occurs most often through reactivation, which can be prevented with prophylaxis with acyclovir in seropositive patients. Most patients will present with shingles, which may result in severe post-herpetic neuralgia, but some may develop chickenpox. Disseminated VZV infection, which may involve the CNS, occurs more frequently in patients with chickenpox, but may also happen after shingles. Other relevant viral infections at this stage are those due to the Epstein-Barr virus (EBV) and JC virus. EBV infection can present with a wide range of severity, ranging from a benign febrile illness, resembling infectious mononucleosis, to a severe neoplastic disease, the post-transplant lymphoproliferative disorder (PTLD) [26]. In PTLD, infection of a clone of B-cells by EBV combined with reduced T-cell surveillance, due to immunosuppressive therapy, results in unrestrained proliferation of the B-cell clone. This lymphoma may spread to extra-nodal sites, including the CNS, either in the form of focal brain lesions or as diffuse lymphomatous meningitis. PTLD has also been associated with para-
neoplastic neurological syndromes: 2 patients with para-
neoplastic neuropathy and anti-Tr antibodies have been re-
ported [15]. PTLD is associated with a very poor prognosis. JC virus infection of the CNS causes progressive multifocal
leukoencephalopathy (PML), a distinct syndrome which
presents with visual, cognitive, and motor symptoms [27].
Brain MRI typically shows multifocal non-enhancing asym-
metric white matter hyperintense lesions in T2 and FLAIR
sequences. DNA of the JC virus can be detected in CSF by
PCR. Prognosis is also sombre. Bacterial infections are rare,
unless there is coexistent GVHD. The most common causa-
tive agents are encapsulated bacteria (Pneumococcus, Menin-
goccus, Haemophylus influenzae), especially in patients
who have not been properly vaccinated. They all may cause
meningitis. Fungal infections include cerebral toxoplasmosis
and meningitis due to Cryptococcus neoformans. Toxoplasma
gondii is an obligate intracellular parasite. It causes opportu-
nistic infections of the CNS in the form of discrete mass lesions
(abscesses) or diffuse meningoencephalitis. Lesions of necro-
tizing encephalitis may also be associated with secondary vas-
cular changes, including vasculitis, oedema, and haemorrhage.

GVHD developing or persisting beyond the 100th day post-
transplant is defined as chronic. This condition emulates
autoimmune diseases. Clinical manifestations will thus re-
semble those of primary dysimmune disorders, such as pro-
gressive sclerosis, Sjögren’s syndrome, systemic lupus, or
primary biliary cirrhosis. The skin and mucosae are often in-
volved. Patients may develop lichenoid lesions, sicca syn-
rome, and malar rash. Other systemic manifestations include
arthritis, obliterative bronchiolitis, and cholestasis. Neuro-
logic complications are common and involve most frequently
the peripheral nervous system: polyneuropathy, myasthenia gravis,
neuromyotonia, and acute or chronic demyelinating neuroopa-
thies. Treatment follows the same guidelines used for their
primary autoimmune counterparts, combined with basal treat-
ment for chronic GVHD. Rarely, chronic GVHD may affect
the central nervous system in the form of cerebral angiitis
[28].

Conclusions

Neurologic complications of HSCT are frequent. As the
use of these procedures expands and their indications
widen, the prevalence of these complications is expected to
increase. Diagnosis of the neurological problems in this
setting is difficult and requires for the physician to be fa-
miliar with the steps of the procedure, the most common
medical complications, the treatments employed, and their
possible adverse reactions. Research is important, not only
to optimize prevention and treatment of these often devas-
tating complications but also to help understanding the
mechanisms underlying dysimmune disorders and the bio-
logical interactions between stem cells and the nervous
system, which might eventually allow for the development of
regenerative therapies for the neurological disorders.

Conflict of Interest

None.
Are You Interested in Performing Cochrane Reviews in Neuro-Oncology?

Robin Grant¹, Michael Hart², Gail Quinn³

Abstract: In this article, we describe the newly formed Cochrane Neuro-Oncology webpage, which is a simple, fast source to find all Neuro-Oncology-related Cochrane Reviews. We describe where the reviews have been produced and identify areas where no high quality systematic reviews of randomised controlled trials exist. The Cochrane Collaboration is a world-wide, not-for-profit organisation which has information on > 0.6 million randomised controlled trials across all areas of healthcare. We describe the requirements for production of a Cochrane review, online help available, and personal support for prospective reviewers, available through the Cochrane Gynaecological and Orphan Cancer Review Group. Eur Assoc of NeuroOncol Mag 2012; 2 (2): 84–7.

Key words: evidence-based, randomised controlled trial, review, brain, central nervous system

Introduction

Neuro-oncologists need to be able to source best evidence for treatment quickly and understand the limitations of the best evidence. Systematic reviews and meta-analyses are integral to good clinical care, as well as forming the basis for planning health services nationally. Systematic reviews should be published according to an internationally recognised standard.

Cochrane and Reviews

The Cochrane Collaboration is an international, not-for-profit organisation of 28,000 people from over 100 countries, who work together to provide the best available clinical evidence for health professionals and the public (http://www.cochrane.org/). Resources include: the Cochrane Central Register of Controlled Trials database (CENTRAL) with over 600,000 records of randomised trials, technology assessments, economic evaluations, methods studies, and systematic reviews.

Cochrane systematic reviews and meta-analyses are recognised as the highest standard in evidence-based health care. Reviews investigate the effects of interventions for prevention, treatment, rehabilitation, and diagnosis. It has an Impact Factor of 5.653 for the 4600 systematic reviews that it publishes on the Cochrane Library website (http://www.thecochranelibrary.com/view/0/index.html).

Evidence-Based Neuro-Oncology

Cochrane organises their reviews through Collaborative Review Groups (CRGs). For the last 10 years, Neuro-Oncology reviews have been produced with the support of the Cochrane Gynaecological Cancer CRG, who also support “orphan reviews” from smaller cancer topics. Other CRGs have also published reviews relevant to neuro-oncology. These include the Cochrane Pain, Palliative and Supportive Care Group (PaPaS), Cochrane Epilepsy Group, Depression, Anxiety and Neurosis Group, Neuromuscular Disease Group, and several others.

The neuro-oncology titles found on the Cochrane Library (Figure 1) stand at 36 completed reviews, protocols, or titles (Table 1) from 14 countries across the world (Figure 2). With the introduction of carmustine-impregnated wafers and temozolomide, the Cochrane Library has provided critical appraisal of both these therapies. Interest in established surgical treatments has been generated with findings highlighting the current level of evidence for surgical resection in high-grade glioma and single brain metastasis. From a symptomatic viewpoint, evidence for prevention of seizures and treatment of epilepsy and depression have been performed and highlight the lack of high-quality evidence on which to base advice.

Many areas in neuro-oncology have still to be subjected to appraisal using Cochrane methodology. There are no reviews on the rare tumour types such as primary CNS lymphoma, pineal region tumours, optic nerve glioma, medulloblastoma, or many of the childhood brain tumours. There are not yet re-
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views on the benign intracranial tumours, eg, pituitary tumours, meningiomas, or vestibular schwannomas, despite purported improvements in treatment. There are a few reviews on spinal metastasis, epidural spinal cord compression, and peripheral nerve toxicity with chemotherapy.

**The Webpage**

With the help of the Cochrane Editorial Unit and the Cochrane Gynaecological Cancer CRG, we have established a Cochrane Neuro-Oncology Webpage (http://www.cochrane-gyn-can.org/neuro-oncology). Development of this neuro-oncology webpage has been necessitated by the improving quality of research in evidence-based neuro-oncology and plethora of new reviews. It is aimed at providing a focal point within the Cochrane website to provide a coherent network to locate reviews: this also has the benefit of highlighting what reviews have not been undertaken and what areas would benefit from a Cochrane systematic review. Links are also provided to Cochrane resources to educate and assist new authors. We intend to provide links to the 3 world-wide neuro-oncology associations (European Association of Neuro-Oncology [EANO], Society for Neuro Oncology [SNO], and Asian Society for Neuro-Oncology [ASNO]) and any individual national neuro-oncology associations, who may wish links to identify Cochrane Reviews or who wish to identify areas where reviews are still required.

**Writing a Review**

If you are interested in performing a review, the first stage is to read more about the Cochrane Collaboration from the hyperlinked webpages, and contact the Managing Editor to register interest in the proposed title for the review (gail.quinn@ruh-bath.swest.nhs.uk or clare.jess@ruhbath.swest.nhs.uk). Each systematic review addresses a clearly formulated question; for example: “Can monoclonal antibodies improve survival in glioblastoma multiforme?” All the existing primary research on a topic that meets certain criteria is searched for and collated, and then assessed using stringent guidelines, to establish whether or not there is conclusive evidence about a specific treatment. The reviews are updated regularly, ensuring that treatment decisions can be based on the most up-to-date and reliable evidence. There are several steps to doing a review and support is available at all stages (Figure 3).

All potential authors of Cochrane systematic reviews have access to training and support resources from the Cochrane Collaboration. Complete information about training is provided on the dedicated Cochrane Training website (http://www.cochrane.org/training). The Cochrane Collaboration has centres in every continent and many European countries including UK, Netherlands/Belgium, France, Finland, Norway, Switzerland, Germany, Austria, Italy, and Croatia. There is very frequently a centre in an author’s country of origin, with which relationships for generic education and advice can be sought. Important resources required are noted below:

- The Cochrane Handbook for Systematic Reviews of Interventions is the official handbook and describes in detail the process of preparing and maintaining Cochrane reviews of the effects of interventions (http://www.cochrane.org/training/cochrane-handbook).
- RevMan is the downloadable software used to prepare and maintain Cochrane reviews and find documentation and support (http://ims.cochrane.org/revman).
Diagnostic reviews of accuracy of a test have dedicated resources and support.

Training can be in person via a range of face-to-face workshops around the world, at our annual Cochrane Colloquium which incorporates a varied programme of training workshops as part of the conference schedule, or online in a series of interactive online learning modules (http://www.cochrane.org/tags/news-events/cochrane-collaboration-calendar).

Literature searching: the Cochrane Central Register of Controlled Trials (CENTRAL) is a database of over 600,000 records of randomised trials that is a recommended source for all authors, available through The Cochrane Library (http://www.cochrane.org/cochrane-reviews/about-cochrane-library). Searches are also run on MEDLINE and EMBASE as part of the support offered by the editorial base.

Evaluating the evidence: while the Cochrane Style Resource can compare your review against the official style guide, GRADEpro is a downloadable additional software resource used to create “Summary of Findings” tables for Cochrane reviews, and find documentation and support. PRISMA (formerly QUOROM) gives good reporting guidelines for systematic reviews (http://www.cochrane.org/about-us/evidence-based-health-care/webliography/books/reporting).

Collaborating online and cross-cultural communication guides are available to allow review teams to collaborate remotely and work internationally and across cultures.

Cochrane have a strict policy on commercial sponsorship as it must protect the integrity of reviews and review authors.

The Cochrane collaboration have guidance on co-publication and dissemination of your review that is readily available through the website http://www.cochrane.org/policy-manual/225-publication-versions-cochrane-reviews-print-journals.

Publishing a Neuro-Oncology Cochrane Review can be a lot of work, but, along the way, you will become much more knowledgeable about interpreting the results of trials and understanding evidence-based practice, as well as providing a high-quality review which will be read by policymakers, colleagues, and patients around the world. The future of neuro-oncology is likely to involve the development of individualised therapy and the use of more sophisticated operative techniques; translating these advances into improved clinical outcomes, including greater emphasis on quality of life, will require building on the foundation of the reviews in this collection. There will be a meeting of the Cochrane Neuro-Oncology Interest Group at the 10th EANO Meeting on Friday, September 7, from 11:00–13:00. We hope that you are interested in the possibility of producing Cochrane Reviews or helping with the review process and would be delighted to see you there. Mike Hart will discuss the existing neuro-oncology reviews and the review process while Gail Quinn will describe the training and help available through the Cochrane Gynaecological and Orphan Cancer Review Group. We will look for ideas of areas requiring an evidence-based review. Robin Grant will chair. We look forward to a fruitful collaboration.

Those interested in attending the meeting, please contact Robin.Grant@luht.scot.nhs.uk

Conflict of Interest

The authors state that no conflicts of interest exist.

Acknowledgements

We would like to acknowledge the help of David Tovey, Editor in Chief of the Cochrane editorial unit, London, Clare Jess, Managing Editor, Cochrane Gynaecological and Orphan Cancer Review Group, Bath, and Tracey Bishop, Assistant Managing Editor, Cochrane Gynaecological and Orphan Cancer Review Group, Bath, for their assistance in developing the Neuro-Oncology Cochrane Webpage.
Oncovideos is a series of videos on standard practical procedures related to the various oncology disciplines targeting young oncologists who need practice-oriented training.

Several neuro-oncology departments have contributed to the Oncovideos project by producing videos on standard procedures in neuro-oncology.

The video produced by Dr Guido Cavaletti, University of Milano “Bicocca”, Monza, Italy, and Dr Wolfgang Grisold, Kaiser-Franz-Josef-Spital, Vienna, Austria, on chemotherapy-induced peripheral neurotoxicity (CIPN) shows examples of simple methods of how to perform an objective neurological examination to detect and assess CIPN.

The video produced by Drs Wolfgang Grisold and Stefan Oberndorfer, Kaiser-Franz-Josef-Spital, Vienna, Austria, on CSF in oncology shows the commonly used procedure of lumbar puncture, CSF analysis, and also interventional procedures for intrathecal treatment.

The video produced by Dr Martin Klein, VU University Medical Center, Amsterdam, The Netherlands, on bedside neurocognitive testing in brain tumour patients shows cognitive functions affected in brain tumour patients, how to identify and select tools/approaches for evaluating cognitive function and explains the indications for neuropsychological referral.

Finally, the video produced by Drs Robin Grant and Simon Kerrigan, Edinburgh Centre for Neuro-Oncology, UK, on neurological examination for the oncologist shows the examination of the cranial nerves and limbs and covers the differential diagnosis between direct cancer-related and indirect or treatment-related neurological symptoms and signs.

All videos in the area of neuro-oncology have been peer-reviewed by the European Association of Neuro-Oncology (EANO). All videos are accredited by the Accreditation Council of Oncology in Europe (ACOE), enabling users to collect CME credits.

Coordinated by the European CanCer Organisation (ECCO), the Oncovideos project was launched with financial support from the European Commission and is freely available to all oncology healthcare professionals upon a simple registration process at http://www.ecco-org.eu/oncovideos. The initial series of 25 videos was completed in 2011. ECCO plans to expand the content with additional videos in 2012.

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Background

Brain metastases of solid cancers are frequent and pose a major medical challenge, as they are associated with high morbidity and poor prognosis. The incidence of brain colonization strongly depends on the tumour type, in some cancers also on the molecular subtype [1]. Lung cancers (both small-cell and non-small-cell lung cancer), breast cancer (particularly HER2-positive and triple-negative subtypes), kidney cancer, and melanoma metastasize to the CNS most frequently, while brain metastases from other common cancers, such as prostate or colorectal cancer, are rare. The incidence of brain metastases has been noted to be rising. The reasons are likely multifactorial and include an increasing incidence of lung cancer associated with tobacco consumption, generally longer survival times of cancer patients, and increased use of cranial magnetic resonance imaging in the upfront staging and follow-up. Furthermore, the advent of novel therapeutic compounds with good anti-neoplastic activity but inadequate penetration via the blood-brain barrier (eg, trastuzumab in HER2-positive breast cancer) may also contribute to an increase of brain metastases by “banishing tumour cells into the protected exile CNS”. The therapy of brain metastases currently relies mainly on surgery and radiotherapy (whole-brain and stereotactic/unfractionated radiotherapies). Systemic antineoplastic therapy has shown limited or no efficacy in brain metastases although comprehensive studies are almost lacking [2]. However, recent studies have elucidated some of the aspects of brain metastasis formation and an increasing understanding of the pathobiology of brain colonization supports the development of targeted agents that inhibit brain metastasis formation in high-risk cancer patients or that successfully treat manifest brain metastases [3].

Pathobiology

Metastatic brain colonization involves tumour cell dissemination from primary tumours or extracranial metastases through the blood circulation, attachment to brain endothelial cells, extravasation into the parenchyma, and interaction with the local microenvironment. According to the “seed and soil” concept, brain colonization is driven by a specific affinity of certain tumour cells for the milieu of certain organs. The specific reasons for the variable brain-tropism among tumour types remain unclear although a relation to molecular factors rather than just to the anatomy of blood perfusion has been postulated [4].

Circulating cancer cells attach to brain endothelial cells primarily at vascular branch points and transendothelial migration is probably mediated by interaction of tumour cell surface receptors and endothelial cell adhesion molecules like integrins, selectins, and chemokines. Platelets and leukocytes may support metastasis formation (or are exploited by tumour cells to do so) via selectin-dependent bonding of tumour and endothelial cells [3, 5].

After brain invasion, cancer cells degrade the local extracellular matrix (ECM) by production of heparanase and matrix metallo-proteases to facilitate migration and growth. Resident glial cells including astrocytes and microglia seem to exert not only anti-neoplastic effects like production of inflammatory tumouricidal molecules (eg, nitric oxide), but may also have pro-neoplastic functions. For example, astrocytes have been shown to protect tumour cells upon physical contact and exchange of calcium through gap junctions [6].

Angiogenesis is a major step in brain metastasis formation and involves activation of the vascular endothelial growth factor receptor (VEGF) pathway. Interestingly, the angiogenic potential seems to differ between tumour types. Some tumour types, eg, non-small-cell lung cancer, depend on early neoangiogenesis for successful brain metastasis formation, while others, such as melanoma, tend to spread along existing vessels (so-called “vascular cooption”) [7].

Targeted Therapy Approaches

Effective targeted therapy approaches are emerging for patients with brain metastases. Among them, the most promising include anti-angiogenic drugs, inhibitors of v-RAF murine sarcoma viral oncogene homolog B1 (BRAF) for BRAF V600E mutated melanoma, and inhibitors of the epithelial growth factor receptor (EGFR) for non-small-cell lung cancer. For a long time, anti-angiogenic agents were not studied in brain tumour patients due to concerns of an increased risk for intracranial haemorrhages. However, large meta-analyses did not confirm these concerns and trials studying anti-angiogenic approaches in brain metastases have therefore been initiated. The blood-brain barrier-stabilizing effect of such drugs needs to be taken into account in such studies, as it has an impact on neuroradiological presentation and thus response evaluation. Based on preclinical data, the anti-angiogenic drug bevacizumab may be effective in preventing brain metastasis formation in non-small-cell lung cancer [7].
Mutations of BRAF, most frequently of the V600E type, occur in a broad range of tumour types and are most common in melanoma (approximately 60% of cases). We could recently confirm that the mutation frequency in brain metastases is similar to the mutation frequencies in primary tumours. Furthermore, we detected that the mutation status is consistent in multiple tumour manifestations in individual patients. Emerging clinical data show that novel BRAF inhibitors are remarkably active against BRAF V600E-mutated melanoma including patients with brain metastases [8, 9]. Patient selection for treatment with BRAF inhibitors requires reliable identification of the mutation in tumour tissue samples, either with DNA-based (eg, with the FDA-approved Cobas 4800 BRAF V600 test, Roche) or immunohistochemical techniques. Recently, a monoclonal antibody has been generated, which detects the BRAF V600E mutated protein in routinely formalin-fixed and paraffin-embedded tissue samples, even in cases with only small tumour content [10, 11].

In non-small-cell lung cancer, several case reports and small patient series suggest that inhibitors of epithelial growth factor receptor (EGFR) such as erlotinib and gefitinib are active in brain metastases, particularly in cases with activating EGFR mutations [12, 13]. Interestingly, a lower frequency of CNS progression has been observed in patients with advanced non-small-cell lung cancer after treatment with EGFR inhibitors [14].

Summary and Conclusions
Some aspects of the pathobiology of brain metastases have been elucidated, leading the way to effective prophylaxis and targeted therapy. BRAF inhibitors seem to be effective in patients with brain metastases of BRAF V600E-mutated melanoma, although definite clinical trials comparing this class of drugs to standard therapy are lacking so far. Anti-angiogenic drugs have shown promising results in preclinical studies and seem to be safe in patients with brain metastases, thus warranting the conduct of well-controlled clinical trials. The results of ongoing and future basic research projects will be necessary to inform patients of the further development of rational treatment of brain metastases based on individual tumour characteristics. The design of clinical trials needs to take into account the large diversity of cancer entities associated with brain metastases and should implement molecular stratification factors whenever possible. The choice of adequate endpoints warrants special attention, as novel drugs may be associated with unusual neuroradiological features. Also, the status of extracranial disease needs to be considered and quality-of-life as well as neurocognitive measures should be included in trial protocols. The development of more effective strategies for the prevention and treatment of brain metastases will profit by the formation of strong interdisciplinary and international scientific collaborations.

Acknowledgements and Conflict-of-Interest Statement
Dr Preusser gratefully acknowledges support by an EANO research fellowship grant. He has received travel support, research funding, and lecture honoraria from Roche.

References:

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Introduction

Clinically detected extra-cranial metastases from glioblastoma multiforme (GBM) are quite rare, with an incidence of < 1% reported in the published literature. Among the various reported sites of systemic metastases from GBM, there are few cases of clinically symptomatic bone marrow metastasis. Haematogenous metastases may occur in the bone with the vertebrae being the most common site of bony involvement. Extra-vertebral metastases from GBM are extremely rare.

Case Report

A 26-year-old woman complained of progressive headache over a period of 2 months. A contrast-enhanced MRI of the brain was performed, showing a heterogeneously enhancing lesion in the right temporal lobe. In December 2010, she was operated for a right parieto-temporal lesion. Histology revealed a glioblastoma with no MGMT methylation and no IDH1 mutation. In January 2011, a post-operative brain MRI showed a gross total removal.

She was treated with radiotherapy and concomitant temozolomide and adjuvant temozolomide with standard schedule for 9 cycles. At the end of treatment she presented no evidence of disease.

In November 2011, she complained of low back pain and gait disturbances. An MRI of the spine showed multiple vertebral body alterations and the presence of periradicular tissue at the lumbo-sacral level (Figures 1 and 2). At the cervical level, the MRI showed mild leptomeningeal enhancement (Figure 3). Clinical examination showed no clinical sign of meningeal carcinomatosis.

A radionuclide bone scan performed 2 weeks later demonstrated extensive skeletal lesions (Figure 4). A brain MRI showed no signs of brain recurrence. The patient was submitted to lumbo-sacral biopsy and bone tissue needle aspiration which yielded the diagnosis “diffuse extra-cranial bone metastases from glioblastoma.” The histology documented metastases by glioblastoma multiforme and the immunohistochemical staining showed positivity for GFAP, CD57, and MIB-1.

Figure 1. Spine T1-weighted MRI image showing a diffuse signal alteration in the vertebral bodies plus the presence of tissue at the lumbo-sacral level.

Figure 2. Spine T1-weighted MRI image with gadolinium. The red arrow indicates the epidural tissue in the epidural space at the lumbosacral level.

Figure 3. Cervical spine T1-weighted MRI image with gadolinium showing a mild leptomeningeal enhancement.
tochemistry of the lesion (immunoperoxidase preparation) was positive for glial fibrillary acidic protein (GFAP).

At present, the patient is being treated with fotemustine chemotherapy.

**Comment**

In the present case, the patient was initially thought to have another malignancy causing the diffuse distribution of bone metastases (vertebral, sacral, and iliac bones) and the lack of signs of brain relapse. However, histopathologic confirmation obtained with biopsy revealed highly cellular pleomorphic cells similar to those seen in the primary cerebral glioblastoma multiforme. Therefore, the extensive bone lesions were accepted as extra-neural metastases of GBM and the patient was treated accordingly. The presence of sub-clinical leptomeningeal involvement, however, may explain the vertebral bone diffusion but not the extra-vertebral bone metastases.

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Paraneoplastic Encephalitis, Myelitis, and Posterior Column Degeneration in a Patient with Breast Cancer

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Introduction

Paraneoplastic neurological syndromes (PNS) are rare and have been divided into “classical” and “probable syndromes” according to clinical manifestations and antibody profile. Many PNS are associated with onconeural antibodies, but failure to detect these antibodies does not exclude the diagnosis. Paraneoplastic myelopathies often remain unrecognized and are usually associated with multifocal neurologic involvement. Prognosis and treatment are not well-defined. We report on a patient presenting with a severe affection of the spinal cord in context with a PNS.

Case Report

A 40-year-old woman had been suffering from vertigo and blurred vision for 2 months. Due to progression of the symptoms and ataxic gait, she was admitted to our department. She presented with rotatory nystagmus, diplopia as well as ataxia of the trunk and lower limbs. MRI of the brain was normal, MRI of the spine revealed a myelopathy of the cervical spinal cord. CSF was pleocytotic with 30 cells and oligoclonal bands were positive. Onconeural antibodies and surface antibodies for PNS were negative. High-dose corticosteroids led to minimal and short-lasting improvement. Neuromyelitis optica, sarcoidosis, or a rheumatic aetiology could be ruled out. The newly discovered breast cancer, the oligoclonal bands, and CSF pleocytosis suggest a paraneoplastic origin. The involvement of posterior columns (Figures 1 and 2) is a new observation. Myelopathy is usually part of an encephalomyelitis as described in this case. The prognosis and response to treatment was poor.

Follow-Up

The patient received chemotherapy (doxorubicin and cyclophosphamide) for 6 months. Neurological symptoms did not remit and series with immunoglobulins (IvIG, 0.4 g/kg body weight) had no effect. The patient was discharged and has remained unchanged concerning neurological symptoms. She is severely disabled and still confined to the wheelchair.

Comment

The patient presented with an encephalitic-like onset with nystagmus, diplopia, and myelopathy resulting in apallesthesia. Due to the clinical features and positive oligoclonal bands a severe course of multiple sclerosis was considered. But the pattern of spinal cord alteration and normal findings in the cranial MRI suggested an alternative diagnosis. The newly discovered breast cancer, the oligoclonal bands, and CSF pleocytosis suggest a paraneoplastic origin. The involvement of posterior columns (Figures 1 and 2) is a new observation. Myelopathy is usually part of an encephalomyelitis as described in this case. The prognosis and response to treatment was poor.

Due to ataxia of the trunk and lower extremities the patient was confined to a wheelchair. Finally, a CT scan of the thorax showed an enlarged lymph node in the axilla and biopsy revealed ectopic breast cancer (Her2-neu-protein-negative). A PET scan did not reveal any signs of cancer or metastases, several examinations of the breasts remained unremarkable.

Figures 1 and 2. T2-weighted MRI of the spinal cord: longitudinally symmetric extensive signal abnormalities of the posterior columns.
are not well-defined. The most common cancers associated with paraneoplastic myelopathy are cancers of the breast and lung. According to a recent review [1], paraneoplastic myelopathy results in severe disability and only a minority of patients improve with treatment. The rarity of paraneoplastic syndromes, in particular, paraneoplastic myelopathies, limits evidence of treatment, so knowledge about therapy relies on case reports and expert opinions. This case study could demonstrate MRI changes impressively. Symmetric, longitudinally extensive tract or grey matter alterations are characteristic for paraneoplastic myelopathy.

The classification of this PNS is difficult as the transient encephalitic symptoms, in association with focal myelopathy (posterior column), have neither been observed in the definite PNS [2] nor in association with the recently observed surface antibodies. Graus et al established criteria for definite or possible PNS. According to these criteria, our case has to be classified as possible PNS. The presence of the tumour and neurological symptoms but absent onconeural antibodies and lack of improvement after tumour therapy leads to the classification of a possible PNS.

References:

Further Reading:

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Case Study

A 72-year-old woman presented at her local hospital with headache, vomiting, and a right hemiparesia for the past 5 days. Cranial MRI showed in the left hemisphere a large temporo-parietal mass with 2 enhancing lesions (Figure 1a). As she deteriorated rapidly, she received 80 mg methylprednisolone per day intravenously with rapid resolution of her symptoms. An MRI performed one week later showed a dramatic response (Figure 1b). Methylprednisolone was reduced to 16 mg/day given per os. An exhaustive work-up for presumptive primary central nervous system lymphoma (PCNSL) was negative (thoraco-abdomino-pelvic CT scan, HIV serology, ophthalmologic examination, bone marrow biopsy, CSF analysis). A biopsy targeting the residual enhancing lesion was performed and showed an important macrophagic proliferation with perivascular tropism. Identification of CD20-positive large cells within the perivascular space allowed the diagnosis of diffuse large B-cell lymphoma with post-steroid macrophagic detersion (Figure 2). The patient was transferred to our institution where a high-dose methotrexate-based polychemotherapy was given. The patient achieved a complete response and is still in complete remission 2 years after the diagnosis.

Figure 1. MRI axial T1-weighted sequences with gadolinium injection (a) before steroid administration and (b) after one week of steroid administration major partial response.

Figure 2. Brain biopsy. (a) Large macrophages with a perivascular tropism. (b) High magnification: prominent astrocytic and microglial response without atypical cells. (c) Expression of CD68 by macrophagic cells. (d) Accumulation of large CD20-positive cells within the perivascular space, suggesting a primary, diffuse large B-cell lymphoma with post-corticosteroid macrophagic detersion.
Comment

It is well known that PCNSL is potentially highly sensitive to corticosteroids, which act not only by restoring the impaired blood-brain barrier but also by a specific cytotoxic activity on the lymphoma B-cells [1, 2]. An objective radiological response is achieved in approximately 40% of cases [3] and some authors have suggested that initial response to steroids may be associated with a better prognosis [4]. Tumour shrinkage or disappearance of PCNSL may occur even after a short exposure to steroids (sometimes only after 24 hours). Therefore, unless patients are rapidly deteriorating with suggestive radiological features of PCNSL, it is usually recommended not to give corticosteroids until histological confirmation has been obtained. Recently, in order to determine whether corticosteroid administration before biopsy prevents histopathological diagnosis of PCNSL, the Mayo Clinic conducted a retrospective analysis on their patients who received steroids before biopsy [5]. Interestingly, only 8 patients out of 68 (12%) needed a repeat brain biopsy to confirm PCNSL. In addition, this rate was not significantly different from that observed in patients who had not received any steroids (5 out of 39 patients, 13%). However, in this series, the vast majority of patients were not corticosteroid-sensitive, most of them retaining the original contrast-enhancing lesions on their serial preoperative neuroimaging. In the present case, a major partial response (> 90%) was obtained. The biopsy performed on the remaining contrast-enhancing lesion showed prominent infiltration of macrophages, T-lymphocytes, and reactive gliosis, with apparent lack of large lymphoma cells on haematoxylin/eosin staining. Only a few scattered CD20-positive large cells were detected by immunohistochemistry around vessels corresponding to residual lymphoma tumour cells after steroid response. Hence, if no significant change in contrast enhancement is observed after administration of corticosteroids, a biopsy can be performed with a high probability of yielding a diagnosis. In the case of major partial response, pathological changes induced by steroids may obscure the diagnosis of PCNSL, as illustrated here. Thus, an immunohistochemical or molecular characterization of tumour cells is needed, but since the diagnosis may remain uncertain, tapering corticosteroids and delaying biopsy until tumour regrowth would be a reasonable option.

References:


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For the second time, in the Netherlands a National Brain Tumour day was held on March 17, 2012, and I was invited to speak about “Caring for patients and their carers”. The programme contained presentations of physicians representing the multidisciplinary character of diagnosis and treatment of brain tumour patients as well as a contribution of a patient. In the afternoon, there were sessions in smaller groups with experts, patients, and their carers, addressing various topics such as new treatment modalities, clinical research, and psychosocial care. I would like to share with you what I discussed with the audience consisting of patients, their carers, and brain tumour survivors.

When there is suspicion of a brain tumour the patient and his or her carer meet difficult times of uncertainty and challenges, in awaiting the definitive diagnosis and possible treatment of the brain tumour after resection or biopsy. There is fear of hearing the worst news in a lifetime and there is hope. Hope that treatment will be possible, hope for rehabilitation, hope for a favourable outcome. And if treatment is necessary there is hope to be able to endure treatment, for good results, for an MRI with no signs of tumour, for quality of life. But anxiety and uncertainty remain.

In academic and other neuro-oncology centres in the Netherlands, specialized oncology nurses are part of the multidisciplinary team, available to deliver psychosocial care with a low threshold. Patients and their carers can call or e-mail or just drop by with a question, to help diminish or eliminate anxiety or to talk about experiences in the process of the disease. As part of the multidisciplinary team, the neuro-oncology nurse offers help and guidance throughout the process of the disease and its treatment. During contacts at the outpatient clinic, besides talking about treatment and MRI results, often other subjects are addressed: how to get help in managing difficulties such as hemiparesis, aphasia, and hemianopia; how to cope with personality and character changes such as egocentricity, agitation, inappropriate or impulsive behaviour, lack of insight, loss of initiative, fear, anxiety, depression; practical subjects, such as driving and getting help and support for housekeeping, support within the family, with children, help to discuss the disease and its impact even at school; help and referrals for rehabilitation, adjustments at home, help in taking care of the patient, day and night, help for the carer in taking care for him- or herself. Furthermore, there is the problem of fatigue, addressed by talking about ways of prioritizing activities and being able to maintain contacts. Another subject of dialogue can consist of existential issues and questions, neuro-oncology nurses want to create openness for the patient to be able to talk about the end-of-life phase, and by doing that they hope to take away anxiety and uncertainty.

Having heard the “bad news”, patients often cannot hear, remember, or comprehend what is being said about treatment. What they do remember is that the doctor told them that they will eventually die of their brain tumour. David Bailey was diagnosed with a glioblastoma and survived for 13 years after his initial diagnosis. He advocated giving patients hope so that they would be able to cope in their fight against their brain tumour. I try to give my patients examples of brain tumour patients such as David Bailey, who lived for a long time after diagnosis with good quality of life. It helps them because it gives hope and faith in being able to endure treatment “to beat the brain tumour.”

Patients and their partners have to be able to adjust to the situation of having to deal with a disease, its treatment, signs, and symptoms. They need to be able to set achievable targets, to discuss their problems and, if possible, to find a way to resolve problems. It will help patients to be able to be directive, to have the feeling of control, to manage their lives with the disease. What also attributes to self control is to receive honest information, if necessary, good psychosocial care, and referrals to get the right help at the right time and at the right place. Much information is available at the internet, at web portals of hospitals, of patient support groups, of associations, and societies involved in brain tumour treatment. Relatives will help seek the best hospital, the best doctor, and the best treatment. Some of those treatments will give hope, but others will perhaps give false hope. Some patients state that, “What you don’t know cannot hurt you”, but the question I would like to ask is, “Is all the information found on the internet reliable, comprehensible, and is it possible to translate this to the specific situation of an individual patient?” You could ask yourself what you do want to know and at what time you do want to know.

I have learned from a book I received, written by a patient with a brain tumour treated in The Hague, that not knowing and being able to live her life without constantly being confronted with the possibility that the tumour will recur at some time was her way of having control over her illness. She—a psychology student—was accidentally diagnosed with a low-grade glioma which differentiated a year after the initial diagnosis and she passed away within 4 years. Her diary gives insight into how she coped with her disease and taught me that it is very important for a brain tumour patient to be able to create hope. Besides, I learned that being a neuro-oncology nurse I am not responsible for the disease but I am responsible for the way I inform, guide, and care for the patient.

What if it is no longer possible to hope for cure, if there is no longer the possibility for treatment of the tumour? Then I am responsible for trying to create hope for a chance of being able to set achievable goals, a chance of fulfilling tasks and unfinished business, of doing what is worthwhile to do, of being open about what to expect of the end-of-life phase, create hope that the patient will be able to live his life the way he wants until it is time to say good-bye.

Further Reading:

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EUR ASSOC NEUROONCOL MAG 2012; 2 (2) 97
Disease registries have come a very long way since the 1660s when a Londoner called John Graunt – a prosperous haberdasher by trade – analysed decades of mortality data and literally invented the science of medical registries.

In Graunt’s time, the focus was on bubonic plague and the effects that scourge had on the population’s mortality.

Today, and for a rare disease like a brain tumour, relevant health information collected in national registries and then shared internationally can help ensure accurate analysis of a range of important data.

Primary brain tumours are relatively rare. There are many different types, and currently some countries register only primary malignant brain tumours but do not record benign or low-grade brain tumours.

This discrepancy promoted a UK-based patient organisation, Brain Tumour UK, to launch a 2009 campaign, “Register my tumour, recognise me”, which sought to include the thousands of missing, unregistered brain tumour patients in the UK’s official health statistics.

The importance of registries for all brain tumours is also noted in the Brain Tumour Patients’ Charter of Rights: “I have the right to ask that my brain tumour is properly registered in my country’s cancer registration records, whether it is benign or malignant”.

Also in 2009, the Council of the European Union announced its “Recommendation on an Action in the Field of Rare Diseases” whereby national plans and strategies for responding to rare diseases should be created in each member state by 2013. The importance of registries for rare diseases like brain tumours was recognised in the recommendation.

If we are to understand this fearsome cancer we need to establish methods for pooling consistent data that has been collected by local registries so that we can create an international collaborative brain tumour registry. A first step would be to link local registries and establish limited inter-operability. Over time, the move to internationally standardised datasets and consistent data collection could hopefully be achieved.

Real-World Patient Registries

“Real-world patient registries” – another type of databank but different from population- and hospital-based registries – can provide pragmatic answers to many important questions about a disease trajectory.

While there is currently no consistent definition of a “real-world patient registry”, the term is generally used to refer to data which is dictated by patient experience, namely patient-reported outcomes. Thus, it is an observational attempt to collect information which is then analysed.

Of course, real-world patient registries must also satisfy the same stringent requirements that population- or hospital-based registries do in terms of accuracy, data protection, timeliness, accessibility, good leadership, and well-developed consent mechanisms.

Real-world patient registries can help determine the effectiveness of a therapy post-approval based on reported outcomes from a much larger, far more diverse patient population than is normally available through traditional clinical trials. A brain tumour clinical trial, for example, may only test a therapy on fewer than a thousand people. But a real-world patient registry might keep track of the first 5000 or 10,000 people using the therapy post-authorisation and in everyday life.

Real-world patient registries can also be used for surveillance, flagging up unexpected adverse events in the wider population. They can highlight inequities and inefficiencies in healthcare systems, planning, and resource allocation.

Real-world patient registries can help monitor adherence to guidelines and enhance the quality of patient care because these types of registries track – on a self-reported patient-by-patient basis – exactly how the patient feels about his medical and supportive care.

These registries can also highlight the use of combinations of standard therapies and complementary therapies, as well as record time to diagnosis (thus addressing issues of late diagnosis) and other factors.

Real-world patient registries might even allow us to look at new ways of using existing therapies for new indications and in new combinations.

An Example

One example of a real-world patient registry spanning all brain tumours is the internet-based facility operated by the Musella Foundation in the United States.

Established in 1999, this is a self-reporting registry of brain tumour patients around the world (but mostly from the US) which records and tracks treatments and outcomes of individuals (currently > 800 people) who register online and update their records monthly.

Patients submit pathology and MRI reports; data is anonymised and a consent form is required. Participants may view online anonymised data from other patients and an interactive map reveals where patients are located and geographic trends in treatment.
The success of real-world patient registries relies heavily on people religiously submitting their data and on the efficiencies offered by new technology. On the downside, patients who are elderly or who have no easy access to technological wizardry (as in many of the less developed countries) may not be able to actively participate in a real-world patient registry because of its reliance on high tech.

Four centuries have passed since John Graunt chronicled the devastation of bubonic plague in his scientific pamphlet known popularly and simply as “Observations”\textsuperscript{5}. Graunt, were he alive today, might be surprised at some of the current innovative ways that registry data is being collected and used.

For those whose lives have been touched by a brain tumour, real-world patient registries can play a vital role in patient empowerment and involvement in their own healthcare as well as hopefully achieving improved outcomes.

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Handbook of Clinical Neurology


Soffietti and Grisold as editors together with an all-star cast of academic leaders and expert senior clinicians have contributed 2 remarkable new volumes on „Neuro-Oncology“ to the highly regarded „Handbook of Clinical Neurology“ series published by Elsevier. For nearly 50 years, the Handbook of Clinical Neurology has prided itself on being the quintessential authoritative reference textbook for disorders, diseases, and conditions of the nervous system, and these new volumes, which are dedicated to neuro-oncology, uphold this important tradition. Volumes 104 and 105 will be much sought-after additions to personal and departmental libraries where senior faculty and junior trainees, alike, can enjoy them.

In volumes 104 and 105, the authors address virtually every major topic in the field of neuro-oncology with a particular emphasis on primary brain tumours and their treatment. Although some of the chapters address topics of current interest such as gene and anti-angiogenic therapies, most review more foundational subjects such as the molecular genetic basis of brain tumours, brain tumour pathology, and the roles of surgery, radiotherapy, and chemotherapy in their management. There are strong chapters devoted to each of the major subtypes of primary brain tumours in adults and children, including glioblastoma, medulloblastoma, and low-grade glioma, and also excellent chapters on rare brain tumours, tumours of the peripheral nervous system, ancillary therapies, and clinical trials methods.

A major portion of volume 105 is devoted to thorough reviews of metastatic brain tumours, neurological complications of cancer and paraneoplastic disorders of the nervous system. These chapters are similarly informative and thorough so that the Handbook of Clinical Neurology can now be considered the definitive reference for clinical neuro-oncology.

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<tr>
<td>June 22–23</td>
<td>Best of ASCO Germany</td>
<td>Frankfurt, Germany</td>
<td><a href="http://www.best-of-asco.de/">http://www.best-of-asco.de/</a></td>
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<tr>
<td>June 28–30</td>
<td>MASCCC/ISOO International Symposium on Supportive Care in Cancer</td>
<td>New York, USA</td>
<td><a href="http://www2.kenes.com/masccc/pages/home.aspx">http://www2.kenes.com/masccc/pages/home.aspx</a></td>
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<tr>
<td>June 30–July 3</td>
<td>International Collaborative for Brain Tumor Epidemiology</td>
<td>Montpellier, France</td>
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<tr>
<td>July 7–10</td>
<td>EACR 22 Biennial Congress</td>
<td>Barcelona, Spain</td>
<td><a href="http://www.eacr.org">http://www.eacr.org</a></td>
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<tr>
<td>September 6–9</td>
<td>10th EANO Congress</td>
<td>Marseille, France</td>
<td><a href="http://www.eano2012.eu/index.php">http://www.eano2012.eu/index.php</a></td>
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<tr>
<td>September 8–11</td>
<td>16th Congress of the European Federation of the Neurological Societies</td>
<td>Stockholm, Sweden</td>
<td><a href="http://www2.kenes.com/efns/pages/home.aspx">http://www2.kenes.com/efns/pages/home.aspx</a></td>
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<tr>
<td>September 10–11</td>
<td>Novel Targeting Drugs &amp; Radiotherapy – From the bench to the clinic</td>
<td>Toulouse, France</td>
<td><a href="http://www.estro.org">www.estro.org</a></td>
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<tr>
<td>September 19–21</td>
<td>ESSO 2012</td>
<td>Valencia, Spain</td>
<td><a href="http://www.ecco-org.eu">http://www.ecco-org.eu</a></td>
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<tr>
<td>September 28–October 2</td>
<td>37ème ESMO Congress</td>
<td>Vienna, Austria</td>
<td><a href="http://www.esmo.org/events/_ieenna-2012-congress.html">http://www.esmo.org/events/_ieenna-2012-congress.html</a></td>
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<tr>
<td>October 4–6</td>
<td>48th Annual Meeting of the Austrian Society for Neurosurgery</td>
<td>Graz, Austria</td>
<td><a href="http://www.neurochirurgie.ac.at">http://www.neurochirurgie.ac.at</a></td>
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<tr>
<td>October 5–8</td>
<td>44th Congress of the International Society of Paediatric Oncology</td>
<td>London, UK</td>
<td><a href="http://www.siop2012.org/">http://www.siop2012.org/</a></td>
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<tr>
<td>October 9–12</td>
<td>19th International Congress on Palliative Care</td>
<td>Montréal, Canada</td>
<td><a href="http://www.palliativecare.ca/">http://www.palliativecare.ca/</a></td>
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<tr>
<td>October 13</td>
<td>Autumn Meeting EORTC Brain Tumour Group</td>
<td>Brussels, Belgium</td>
<td><a href="http://groups.eortc.be/brain/">http://groups.eortc.be/brain/</a></td>
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<tr>
<td>October 25–27</td>
<td>12th SIOG Meeting</td>
<td>Manchester, UK</td>
<td><a href="http://www.siog.org/">http://www.siog.org/</a></td>
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<tr>
<td>November 6–9</td>
<td>Molecular Targets and Cancer Therapeutics</td>
<td>Dublin, Ireland</td>
<td><a href="http://www.ecco-org.eu">http://www.ecco-org.eu</a></td>
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<td>November 11–15</td>
<td>Joint Meeting of IPOS, 14th World Congress and COSA’s 39th Annual Scientific Meeting</td>
<td>Brisbane, Australia</td>
<td><a href="http://www.ipos-society.org/ipos2012/">http://www.ipos-society.org/ipos2012/</a></td>
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Meeting Report: EORTC Brain Metastases Strategic Meeting 2012

Matthias Preusser¹, Damien C Weber²

From the ¹Department of Medicine I and Comprehensive Cancer Center CNS Unit, Medical University of Vienna, Austria, and the ²Department of Radiation Oncology, Geneva University Hospital, Geneva, Switzerland

On February 9, 2012, the EORTC Brain Metastases Strategic Meeting 2012 took place in Vienna, aiming to identify potential study designs that may advance therapy of patients with brain metastases. Brain metastases are the most common brain tumours and affect up to 40 % of cancer patients with incidences varying between tumour types and molecular subtypes. Currently, therapy relies mainly on surgery and radiotherapy (whole-brain radiotherapy and/or stereotactic radiosurgery-fractionated radiotherapy). The pathobiology of brain metastases is only partially understood so far, but recent advances have identified potential drugable targets such as the V600E-mutated BRAF protein in melanomas, HER2 in breast cancer, and EGFR in lung cancer brain metastases. Brain metastasis pathway analysis could be studied by investigating the effects of selected drugs in the preoperative setting for oligometastatic patients not requiring emergency surgery. This exploratory methodology for identifying pathway activation and drug penetration may be a new paradigm for biomarker-driven clinical trials for brain metastases. The meeting featured lectures by 15 international experts, who elucidated aspects of trial design, study endpoints, pathobiology, and provided up-to-date information on the trial landscape in the most common tumour types spreading to the brain with a focus on breast cancer, lung cancer, and melanoma (Table 1). After these lectures, potential study initiatives were discussed in a workshop session. Over 60 attendees took part in the meeting and made it a lively and stimulating scientific event.

The lectures and discussions made clear that there is a great need for well-conducted trials in the field of brain metastases. Particular attention needs to be drawn to an adequate trial design, which in many cases is complicated by a lack of data on the incidence and the natural course of brain metastases, especially regarding molecular tumour subtypes. This issue may necessitate flexible and adaptive trial designs that allow for modifications during the trial. Of central importance is the selection of sound trial endpoints. So far, radiological readouts have been poorly standardized in brain metastases and there is a need for generation of diagnostic algorithms that also consider novel therapeutics and their impact on neuroimaging features. All trials on brain metastasis patients should include neurocognitive and quality-of-life (QoL) measurements. Various pitfalls have been identified with the latter endpoints, not limited to but including compliance issues, patients’ cognitive impairment, and liberal time windows for QoL evaluation. Proxy measurements for QoL evaluation were discussed for patients in clinical trials and a new QoL questionnaire containing 15 items divided in global health status, functional, and symptom scales, was detailed. In melanomas, recent data from early clinical studies indicate high efficacy of novel drugs such as BRAF inhibitors and ipilimumab against brain metastases. The question of how these drugs compare to standard treatment regimens should be addressed in randomized trials. Furthermore, the appearance of secondary resistant tumours in many patients calls for studies investigating novel multi-targeted agents and strategies in the recurrent setting. In breast cancer, 2 tumour types are characterized by increased propensity for brain colonization: HER2-positive and triple-negative tumours. In these indications, novel radiotherapy regimens such as whole brain radiotherapy with hippocampal sparing may provide feasible and safe options for brain metastasis (BM) prophylaxis or therapeutic management. Alternatively, patients with diagnosed BM could be treated systemically: a potential phase-III trial could randomized HER-2-positive breast cancer patients to WBRT vs lapatinib plus capcitabine. In addition, novel compounds have been promising in preclinical and early clinical studies and provide promising trial opportunities. In non-small cell lung cancer, trials evaluating whole-brain radiotherapy and EGFR inhibitors as well as optimal palliative approaches are ongoing. Based on preclinical data, prophylactic administration of anti-angiogenic agents may be feasible in this tumour type. The feasibility, the high-cross-over rate, and the potential toxicity of systemic treatment were discussed during the meeting.

In summary, several brain metastasis study designs in breast cancer, lung cancer, and melanoma were discussed which could be potential EORTC prospective trials. A bevacizumab

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**Table 1. Speakers and meeting programme.**

<table>
<thead>
<tr>
<th>Speaker</th>
<th>Topic</th>
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<tbody>
<tr>
<td>Frank Winkler (Heidelberg)</td>
<td>Biology of brain metastases and translational research</td>
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<tr>
<td>Laurence Collette (Brussels)</td>
<td>Trial design</td>
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<tr>
<td>Sven Haller (Geneva)</td>
<td>Response evaluation</td>
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<tr>
<td>Sandrine Marreaud (Brussels)</td>
<td>Challenges to developing a brain met trial</td>
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<tr>
<td>Riccardo Soffietti (Torino)</td>
<td>Endpoints</td>
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<tr>
<td>Martin Klein (Amsterdam)</td>
<td>Neurocognitive function</td>
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<tr>
<td>Jaap Reijneveld (Amsterdam)</td>
<td>Quality of life</td>
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<tr>
<td>Jörg-Christian Tonn (Munich)</td>
<td>Surgery</td>
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<tr>
<td>Brigitta Baumert (Maastricht)</td>
<td>Radiotherapy</td>
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<tr>
<td>Paula Mulvenna (Newcastle)</td>
<td>NSCLC</td>
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<tr>
<td>Dirk Schadendorf (Essen)</td>
<td>Melanoma: BRAF inhibitors and ipilimumab</td>
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<tr>
<td>Renata Duchnowska (Warsaw)</td>
<td>Biomarkers predictive for brain relapse in HER2-positive patients</td>
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<tr>
<td>Nancy Lin (Boston)</td>
<td>Lapatinib</td>
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<tr>
<td>Yazid Belacemi (Paris)</td>
<td>PCI for high-risk patients</td>
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<tr>
<td>Jacek Jassem (Gdansk)</td>
<td>Triple-negative breast cancer</td>
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</table>
prophylactic trial for high-risk lung cancer patients and a WBRT vs capecitabin plus lapatinib phase-III trial for high-risk HER-2 breast cancer could be foreseen. Alternatively, a prophylactic WBRT with hippocampal sparing and concomitant trastuzumab trial could be developed for these patients. Finally, a BRAF inhibitor study for metastatic melanoma could be developed for patients with 1–3 (focal radiotherapy) and > 3 brain (WBRT) metastases.

## Acknowledgements

The meeting was kindly supported by Roche, Novocure, Merck Serono, and the Comprehensive Cancer Center at the Medical University of Vienna.

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Interesting new data were reported during the ASCO 2012 Meeting from June 1–5, 2012, in the field of gliomas, anti-angiogenic agents, and primary CNS lymphomas (PCNSLs).

Cairncross et al (abstract # 2008b) and van den Bent (# 2, plenary session) presented the updated analyses of the RTOG 9402 and EORTC 26951 phase-III trials comparing radiation alone versus radiation + PCV in newly diagnosed anaplastic oligodendrogliial tumours. Both studies showed that the addition of PCV (either neoadjuvant or adjuvant) to radiation significantly improves both PFS and OS in the subgroup of patients with 1p/19q co-deletion, while having no impact in non-co-deleted tumours. This means that radiotherapy alone is no more the standard treatment for 1p/19q co-deleted tumours, and different scenarios regarding chemotherapy, such as drug choice (PCV, temozolomide) and sequence with radiotherapy (before, concurrent, after) are now open.

Wick et al (# 2000) analyzed the role of MGMT promoter methylation within the German phase-III trial on elderly patients with malignant astrocytomas (NOA-08). This trial showed that temozolomide is not inferior to radiotherapy as initial treatment, and MGMT promoter methylation is a strong predictive factor significantly correlated with increased survival in patients with MGMT-methylated tumours receiving temozolomide.


The papers on antiangiogenic therapies in glioblastomas were aimed to answer 2 important questions: (1) who benefits mostly from anti-VEGF agents (bevacizumab, cediranib) and (2) why do these treatments fail? With regard to the first question, Gerstner et al (# 2009) analyzed the patients in a phase-I–II trial on newly diagnosed glioblastomas treated with cediranib and reported that patients with an early increase of perfusion after treatment have improved survival, and baseline plasma SVEGFR1 levels appear to be a potential biomarker of efficacy. Emerson et al (# 2010) and de Groot et al (# 2011) reported preliminary data suggesting as mechanisms of resistance to anti-VEGF agents an increase of macrophages and myeloid cell infiltration, respectively. Thus, targeting macrophages or pathways involved in myeloid cell infiltration could be investigated in future clinical trials.

Two interesting studies on low-grade gliomas were reported. A multicentre phase-II trial of the AINO (Italian Association of Neuro-Oncology; Rudà et al, # 2037) showed that among grade-II oligodendrogial tumours the use of dose-dense temozolomide as initial treatment after surgery significantly improves the control of epilepsy, but not the response rate on MRI as compared to histological controls. Moreover, there is no difference in response between MGMT-methylated and -unmethylated tumours.

Theeler et al (# 2022) reported the largest retrospective series (from the MD Anderson Cancer Center) so far on pilocytic astrocytomas of the adult: from the analysis it emerged that hemispheric tumours in adults behave more aggressively than in paediatric patients and the response to radiotherapy is limited.

A major problem in PCNSLs is the need to reduce the late neurotoxicity from whole-brain radiotherapy (WBRT) without compromising treatment results. Two phase-II studies from the Memorial Sloan-Kettering Cancer Center (Curry et al, # 2006; Omuro et al, # 2008) reported interesting preliminary results in patients achieving a complete response after induction of chemotherapy with methotrexate-based regimens by reducing WBRT or high-dose chemotherapy with stem cell rescue as a consolidation therapy. Roth et al (# 2007) further analyzed the data of the G-PCNSL-SG1 German trial and concluded that elderly patients in complete response after induction of chemotherapy require maintenance treatment.

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The Latin American Neuro-Oncology Network, RedLANO, is a non-profit organization developed with the mission to engage regional specialists in developing basic, translational, and clinical research on neuro-oncology, and to serve as a source of educational content. After completing 2 years of operation, the RedLANO has produced encouraging achievements regarding the number of participating members, which currently amounts to more than 320. There has been a 355-% growth in new users’ participation and the official website, http://www.redlano.org, has received more than 119,000 visits since its set-up in 2010 (noticeable growth happening from September 2011 onwards). The RedLANO platform received 26,000 visits between December 2011 and January 2012, such traffic becoming concentrated after the publication of the preliminary programme for the next congress which will be held in August 2012 in Panama City. Compared to January 2011, the number of visits has increased by 80 %, thereby suggesting an exponential growth throughout this year.

Most RedLANO users come from Colombia, Ecuador, Peru, México, Costa Rica, Chile, Argentina, Bolivia, Spain, the USA, Panama, Paraguay, Puerto Rico, Uruguay, and Venezuela. Our community has managed to run 2 successful congresses and many regional meetings, encouraging and promoting knowledge regarding neuro-oncology and its related areas. Since its establishment, and as a result of the joint work by many specialists, the news section has been strengthened by the images in neuro-oncology and the interactive presentation of conferences; this segment currently offers more than 60 readily addressed products and high-quality content which is being constantly renewed.

RedLANO has also promoted the formation of a monographic follow-up record for patients suffering from high-grade gliomas, currently including more than 220 patients. The preliminary results for 171 patients having a mean age of 56 years (range: 17–84), males predominating (56 %), were presented during the ASCO meeting 2011. 82 % of the patients had glioblastomas (most being primary ones); 59 % of them were treated by cytoreduction and a biopsy was performed on 23 % of them. 77 % of the patients completed the treatment scheme proposed by Stupp et al [1], involving a 58.2-Gy median radiation dose and an average of 5 ± 3 temozolomide cycles (excluding concomitance). Pseudoprogression was found in 20 % of the patients, median overall survival (OS) was 15.8 months (11.9–19.7 months; 95-% CI) and progression time was 4.1 months (2.9–5.3 months, 95-% CI). The survival rates at one and 2 years were 69 % and 31 %, respectively; retrospective analysis revealed that patients aged less than 50 years (p = 0.0001) had a more prolonged OS as they had a better postoperative functional state (p = 0.05) and better stratification according to the RPA classification (p = 0.04). Seventy-one patients (41 %) were treated with second-line treatment at the time of progression (combinations with bevacizumab [32], temozolomide in dense or metronomic doses [24], BCNU [14], or others [1]), achieving 66 % overall response by adding anti-angiogenic therapy and 76 % clinical benefit [1]. The state of the MGMT promoter methylation gene was evaluated in 93 patients, revealing a 15.8-month (9.0–22; 95-% CI) OS in the segment of positive patients compared to 7.6 months (5.5–9.6; 95-% CI) for those who proved negative. The latter difference was statistically significant (p = 0.001) [2].

These achievements have shown RedLANO’s transition towards maturity, encouraging the organisation to continue promoting advances in neuro-oncology through research and education. It is hoped that neuro-oncology will be able to integrate specialists in Latin-America during this year.

References:

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**The Collaborative Ependymoma Research Network (CERN)**

Mark R Gilbert

Department of Neuro-Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

CERN was launched in 2007 as a unique multi-disciplinary collaborative effort of international investigators guided by the mission to develop new treatments for ependymoma, improve the outcomes and care of patients, ultimately leading to a cure; CERN combines efforts from investigators with expertise in adult and paediatric brain tumour research. Mark Gilbert serves as the overall leader of CERN, and 5 projects define the core structure.

The first project is the Clinical Trials Network encompassing groups of paediatric and adult centres of excellence, led by Amar Gajjar and Mark Gilbert; it now includes European sites as well. Currently, several clinical trials are open and actively accruing including 2 adult trials and 2 paediatric studies (Table 1).

The second project is the Pathology and Tumour Molecular Profiling project. Adult and paediatric neuropathologists, Ken Aldape and Cynthia Hawkins, lead this project and provide central review of tumour tissue for clinical trials. Additionally, a tumour repository has been established that collects confirmed ependymoma tumour samples that have good clinical outcomes annotation providing a great resource for molecular discovery and for studies of patient outcomes.

The third project is Drug Development and Discovery. This project is led by the combined efforts of a basic/translational scientist, Richard Gilbertson, and a medicinal chemist, Kip Guy. High throughput screening using a robust ependymoma model has already identified several candidate agents, including 5-fluorouracil that is currently in clinical trial. Collaboration with the Pathology Project will focus on developing specific profiles in patient’s tumours that inform treatment decisions.

The fourth project is Tumour Biology, led by Richard Gilbertson. This project has focused on developing robust models that recapitulate the heterogeneity of ependymoma so that drug screening can be performed on the spectrum of ependymoma and potentially permit treatment optimization for each patient. Collaboration with the molecular profiling effort in the Pathology Project will help validate these models and create clinically relevant profiles.

The fifth project focuses on Patient Outcomes and is led by Terri Armstrong. This project has successfully incorporated informative measures of patient’s performance and symptom burden into the current clinical trials. Additionally, outcomes surveys have been launched to assess the spectrum of treatments and care provided to ependymoma patients and to determine the spectrum of disease outcomes in the broad patient population including those without active disease.

Future initiatives include the development of a registry which will track disease course and identify correlutive tumour markers in patients with ependymoma.

These efforts are complimented by an extensive Education and Outreach effort, led by Charles Haynes and Kimberly Wallgren. This effort includes an annual Ependymoma Awareness Day, a robust website containing patient and caregiver resources, and an educational video collection (Youtube.com: search “CERN”). Those interested in learning more about CERN are encouraged to contact Dr Gilbert, any of the project leaders, or submit a query to us through the website: www.cern-foundation.org.

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As part of on-going efforts to forge a closer relationship between the European Association for Neuro-Oncology (EANO) and the US-based Society for Neuro-Oncology (SNO), each organization will feature reciprocal “meet-the-experts” sessions at their respective meetings this autumn.

The EANO meeting in Marseille in September will feature a session chaired by Ken Aldape (Houston) and Riccardo Soffietti (Turin) entitled, “Update in Neuro-Oncology”. This session will cover the following topics:

– What is the right place for bevacizumab: at recurrence or in upfront treatment?  
  Susan Chang, San Francisco
– Biology of resistance to antiangiogenic therapies  
  Michael Weller, Zurich
– Is there a role for dose-dense temozolomide?  
  Mark Gilbert, Houston
– Outcome predictors in low-grade and anaplastic gliomas  
  Wolfgang Wick, Heidelberg

Correspondingly, the SNO meeting in Washington, DC, in November will feature a special joint EANO/SNO “meet-the-experts” session moderated by Riccardo Soffietti and Mark Gilbert entitled, “From Guidelines to New Trials in Low-Grade Gliomas: The American and European Views”. The session will cover the following topics:

– What is the role of awake surgery?  
  Mitchel Berger, San Francisco, and Hugues Duffau, Montpellier
– What is the role of chemotherapy?  
  David Schiff, Charlottesville, and Riccardo Soffietti, Turin

In addition to the “meet-the-experts” sessions noted above, this year the leadership of both organizations established a reciprocal travel scholarship to allow young investigators to travel to each other’s meetings. A combined EANO/SNO committee graded the submitted abstracts, selecting 2 from each organization.

From EANO:
– Florien Boele, Amsterdam: Augmenting quality of life and mastery of informal caregivers of high-grade glioma patients: A randomized controlled trial
– Anna Berghoff, Vienna: Signal intensity in preoperative diffusion-weighted imaging correlates with survival times in patients with single brain metastasis

From SNO:
– Justin Lathia, Cleveland: Identification of a glioblastoma stem cell-specific communication mechanism that drives malignancy and is amenable for therapeutic targeting
– Sameer Agnihotri, Toronto: Elucidation of DNA repair signatures that confer resistance to temozolomide and poor survival in patients

Travel scholarship recipients will present their research as a guest of the host organization during the upcoming meetings. The leadership of both EANO and SNO look forward to exploring additional ways to expand interorganizational collaboration in future.

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Interview with Dr Damien Weber about the Atypical and Anaplastic Meningioma Trial

Ufuk Abacioglu

From the Department of Radiation Oncology, Neolife Medical Center, Istanbul, Turkey

Q: Dr Weber, can you tell us about the ongoing “Atypical and Anaplastic Meningioma” trial? What are its rationale and background?
A: A number of retrospective studies have shown that patient outcome is improved when the radiation dose is escalated for non-benign (ie, WHO grade-II/III) meningiomas. The objective of the EORTC 22042-26042 study is thus to assess the impact of high-dose radiation therapy on progression-free survival.

Q: How is the trial designed and what are the inclusion criteria?
A: To be included in the study, patients must be between 18 and 70 years of age with good performance status (WHO 0–2) and present with a tumour of non-benign histology. The meningioma may be located anywhere except in optic nerves. In addition, patients must not have very deteriorated neurological function (NF score 2) and must not have had any prior cancer nor any previous irradiation to the brain. Once in the study, the patient receives the irradiation. The radiation dose (60 vs 70 Gy) is selected as a function of the extension of the tumour resection: 60 Gy for complete resection and otherwise 70 Gy (ie, Simpson 1–3 vs 4–5).

Q: To my knowledge, this is the first prospective trial in this rare disease. Is that correct?
A: Absolutely, this trial is the first prospective trial to be initiated in a cooperative research group. It was an endeavour, as the activation of the 22042 trial followed after the failure of a phase-III trial for benign meningioma (EORTC 22021-26021). This trial was stopped due to poor accrual. Later, the Radiation Oncology Group initiated an observational/therapeutic phase-II trial (RTOG 0539). Both prospective trials are accruing well.

Q: Which groups, countries and how many centres participate in the trial?
A: Twenty-five sites from 7 countries recruit to the trial: Belgium, France, Spain, Switzerland, the Netherlands, Italy, and United Kingdom.

Q: Did you have any stratification factors?
A: No, the study is not randomized but the cohorts and doses are specific to the WHO grade (II vs III) and the extent of the surgery (based on Simpson’s classification) as explained.

Q: Is there a specific quality assurance programme for radiotherapy in the trial?
A: Quality assurance (QA) will be performed by the Image-Guided Therapy Center – Advanced Technology Consortium (http://atc.wusf.edu/) in the US. Prospective Individual Case Reviews (ICRs) are mandatory for each patient included in this trial. All centres are credentialled by a Dummy Run submission prior to trial activation. This is also the first prospective trial using a QA digital platform, eCRFs, and prospective ICRs.

Q: Do you have any translational or biological investigation in this trial?
A: Yes, biological materials are prospectively collected for future research.

Q: There was an amendment regarding the inclusion criteria during the study. Can you tell us about that?
A: First, the sample size for Simpson 1–3 WHO grade-II disease has been increased from 25 to 54 patients. Second, we did remove the statistical objectives for the rare group of patients with Simpson 4–5 WHO grade-II disease, which became part of the observational study. Finally, the delay between surgery and the start of radiotherapy is less stringent with the last amendment, but should be kept at less than 6 weeks. However, in exceptional circumstances up to 8 weeks are allowed prior to HQ approval.

Q: How is the accrual ongoing and when do you expect to reach the accrual goal? When can we expect to see the first results published?
A: The trial has accrued ¾ of its planned cohort of Simpson 1–3 WHO grade-II patients. First results should be available in 2015.

Thank you very much.

Damien Weber is the study coordinator for the EORTC 22042-26042 trial entitled, “Adjuvant postoperative high-dose radiotherapy for atypical and malignant meningioma: a phase-II and observation study.”

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Cognitive Functions in Primary CNS Lymphoma after Single or Combined Modality Regimens


In the January issue, Correa and co-workers reported a comparison of cognitive function in patients with primary central nervous system lymphoma, looking at patients who were treated either with chemotherapy alone or with chemotherapy plus whole-brain radiotherapy. Not surprisingly, these 50 patients, examined in remission, revealed better cognitive function in chemotherapy-alone-treated patients, and the cognitive impairment in the irradiated patients often interfered significantly with quality of life. This study confirms many previous observations and provides also further support for the conclusion of the large randomised phase-III trial [Thiel E et al, Lancet Oncol 2010; 11: 1036–47] that proposed to withhold whole-brain radiotherapy from the primary treatment of primary central nervous system lymphoma.

Relevance of T2 Signal Changes in the Assessment of Progression of Glioblastoma According to the Response Assessment in Neurooncology Criteria


The RANO criteria were introduced to meet the concerns that the classical Macdonald criteria are no longer useful in the area of antiangiogenic treatment. In the February issue, Radbruch and colleagues from Heidelberg, Germany, examined the impact of using RANO criteria in the follow-up of glioblastoma patients. They observed initial T2 progression in 35 of 144 patients when they used an increase of 15 % of the T2 signal area as a cut-off for progressive disease. An increase in the T2 lesion predicted progression on T1 sequences with contrast enhancement. More diagnoses of progression were made when considering T2 sequences, but this was not related to the use or non-use of antiangiogenic therapy. Accordingly, progression without increasing contrast enhancement is likely to be part of the disease course unrelated to a specific type of treatment.

Consensus on the Role of Human Cytomegalovirus in Glioblastoma


In the March issue, the editors decided to publish a symposium report addressing one of the more controversial issues in neuro-oncology, that is, the role of human cytomegalovirus (HCMV) in glioblastoma. Several groups have reported the expression of HCMV nucleic acids and proteins in glioma tissues. Clinical trials exploring potential anti-CMV agents as well as vaccination approaches against CMV have been discussed based on these findings. Yet, many issues regarding these reports of an association of CMV with glioblastoma have remained quite controversial. Specifically, infectious virus particles have never been harvested from glioblastoma tissues. While CMV may induce a number of alterations in human cells that are also seen in various types of cancer, not only glioblastoma, the claim of “oncomodulation,” as made in this conference report, seems somewhat premature. Nevertheless, this consensus conference report is an interesting summary of thoughts of colleagues who believe in a relevant biologic role of this virus in the aetiology or pathogenesis of glioblastoma. It will be interesting to evaluate in a few years from now what is left of the consensus and expectations that were reached at this conference.
The Society for Neuro-Oncology is already hard at work planning its 17th Annual Scientific Meeting and Education Day, which will be held November 15–18, 2012, at the Washington, DC, Hilton Hotel.

As in years past, the meeting will begin with an Education Day where attendees can catch up on timely and relevant topics from the field. Education Day co-chairs Vinay Puduvalli and Balveen Kaur are developing a program entitled „Targeted Therapies Against Primary Brain Tumours“, which will feature 3 sessions: Signal Transduction Agents, Immunotherapy, and Biological Therapies and Stem Cells. Each session will provide a comprehensive review of each topic, from development to clinical application. Immediately following the Targeted Therapies session, there will be a 2.5-hour course on biomarkers, organized by Susan Chang and Ken Aldape. This course will review the definition and potential roles of biomarkers as it pertains to neuro-oncology, the various types of biomarkers, the importance of biostatistical considerations in the development and validation of biomarkers, application of biomarkers in drug development, and the clinical application of biomarkers including their role in the use of anti-angiogenic treatments and future directions.

Running concurrently with Education Day will be a special focused session on quality of life organized by Michael Glantz. This session will cover a number of important topics, including neurocognitive testing, symptom management, novel diagnostic and therapeutic interventions as well as defining and measuring quality of life.

In addition to the accepted oral and poster presentations, the main scientific portion of the meeting, chaired by Nino Chiocca, will feature a number of informative Sunrise Sessions. In the planning stages are sessions on neurofibromatosis, microRNA, energetics and metabolism, emerging neurodevelopmental targets, oncolytic viruses, radiobiology, pituitary tumours, and the biology of brain metastases. And in what is sure to be one of the highlights of the meeting, SNO is pleased to announce that Bert Vogelstein will be delivering the Plenary Keynote Address on Friday, November 16. Consistent with prior meetings, there promises to be high-quality abstracts on a variety of topics related to neuro-oncology for poster and platform presentations. Members of EANO interested in submitting their research for the SNO annual meeting should note the abstract submission deadline of May 15, 2012.

The organizers are also developing a number of sessions for Young Investigators, including a Young Investigators reception, roundtable discussion with senior SNO members, and a post-meeting networking session.

Starting in May, SNO will also be accepting applications for travel scholarships to our annual meeting for professionals living in developing regions of the world. A total of 8 scholarships will be awarded to individuals in the following geographical regions (one per region): Central America & the Caribbean, Central and Southern Africa, China & associated countries, Eastern Europe, Far East and Australasia, Indian Sub-Continent, North Africa & the Middle East, and South America.

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For more information on the Society for Neuro-Oncology, please visit our website, http://www.soc-neuro-onc.org
The Asian Society for Neuro-Oncology (ASNO): History and Activities
Masao Matsutani
Asian Society for Neuro-Oncology, Saitama, Japan

The memorable first meeting of the Asian Society for Neuro-Oncology (ASNO) was held in Kumamoto, Japan, in November 2002. It was a big product by the earnest request from the organizing committee of the first meeting of the WFNO (World Federation for Neuro-oncology) in October 2001.

The first ASNO meeting was organized by brain tumour societies or neuro-oncology societies in 5 countries (Japan, Korea, China, Taiwan, and Turkey) and featured 142 presentations.

The meeting was held every year until the fourth one to distribute "neuro-oncology" among Asian countries, and from fifth meeting it was held every 2 years. The second meeting was held in Seoul, Korea, in 2003, the third was in Shanghai, China, in 2004, the fourth took place in Taipei, Taiwan, in 2005, and the fifth in Istanbul, Turkey, in 2007, with the number of participating countries gradually increasing. We welcomed scientists, physicians, and people in various fields from Malaysia, Singapore, Hong-Kong, the Philippines, India, Indonesia, and other countries.

Consistently from the start, the main subject matter of ASNO has been focused on diagnosis, treatment, pathology, and biology of malignant brain tumours, especially malignant gliomas. A major aim of ASNO meetings is, of course, to discuss the recent advances in the treatment and biology of malignant brain tumours. Another aim is to offer participants understandings of standard "neuro-oncology" and information concerning "what is now ongoing in the world". These advanced or educational lectures were made not only by ASNO members but also by invited guests from the USA and European countries, and they greatly stimulated participants, resulting in increasing interest for neuro-oncology in their own countries.

The highlight at the dawn of ASNO was the 6th meeting jointly with the 3rd Quadrennial Meeting of the World Federation of Neuro-Oncology in Yokohama, Japan, in 2009. The number of participants from ASNO (414) was the largest compared to that from EANO (158) and SNO (100). Even excluding the participants from Japan, the host country, there were 176 participants from 13 Asian countries, including Uzbekistan and Kyrgyzstan.

After the 6th meeting, we decided to hold the meeting every year again because many Asian countries wanted to have the ASNO meeting in their own countries. It has a great impact to have the ASNO meeting in countries where the national neuro-oncology society has not enough power to distribute the standard understanding of neuro-oncology to every corner of the country.

Next year, in 2013, the 10th ASNO meeting will be held in India; it will be the first meeting outside the 5 founding countries.

ASNO has been a virtual society without bylaws or membership fees. Asia is extremely wide between its eastern border (Japan) and its western border (Turkey), and between its northern border (Kazakhstan or Mongolia) and its southern border (Indonesia). Asia comprises 50 countries. We have to travel farther to attend the ASNO meetings compared to EANO or SNO members to attend their respective society meetings. Asian countries are facing different political, economical, and medical situations. Actually, only 19 of 50 Asian countries have participated in past meetings. An ASNO meeting containing all Asian countries still remains in the far distance.

In 2012, a neuro-oncology group from Australia joined ASNO and some newly participating countries have raised their hands to host the meetings after 2014. Taking this opportunity, we started to construct the basic structure of ASNO, including bylaws.

ASNO is expected to promote neuro-oncology in all Asian countries and to build up a close and friendly connection with EANO and SNO to contribute to the development of neuro-oncology.

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