Biol Blood Marrow Transplant 23 (2017) 388–397

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Review

Neurologic Complications after Allogeneic Hematopoietic Stem Cell Transplantation

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Article history:
Received 6 October 2016
Accepted 20 December 2016

Key Words:
Hematopoietic stem cell transplantation
Central nervous system
Cyclosporine
Cerebral aspergillosis
Viral encephalitis
Neurological complications

A B S T R A C T

Neurologic complications after hematopoietic stem cell transplantation are frequently life-threatening, and their clinical management can be highly challenging. A wide spectrum of causative factors—including drug-related toxicities; infections sustained by virus, bacteria, or invasive molds; metabolic encephalopathy; cerebrovascular disorders; immune-mediated disorders; and disease recurrence—may lead to potentially lethal complications. Moreover, given that some neurologic complications are not uncommonly diagnosed post mortem, their overall incidence is likely to be underestimated. Their prompt recognition and timely treatment are of paramount importance to reduce the risk for transplantation-related death.

INTRODUCTION

As the total number of hematopoietic stem cell transplantations (HSCTs) has steadily increased in recent years [1], many complications have become more frequent despite improvements in supportive care. The introduction of less-toxic conditioning regimens [2] allowed the expansion of HSCT to more fragile elderly recipients [3], who are more prone to developing post-transplantation complications. From a clinical standpoint, neurologic complications vary widely both in incidence, ranging from 3% to 44% [4,5], and in severity, ranging from mild transient disorders to serious clinical illness [6]. Causative agents and factors include, among others, neurotoxic drugs, infectious pathogens, metabolic encephalopathy, cerebrovascular illness, and immune-mediated diseases (Table 1).

Neurologic complications may be classified by their time of onset as pre-engraftment, early post-transplantation, and late post-transplantation (Table 2). Early complications are usually associated with drugs used in the conditioning regimen, whereas later events are often due to post-transplantation immunodeficiency. Allogeneic HSCT-associated thrombotic microangiopathy and post-transplantation lymphoproliferative disorders are clinical entities with frequent CNS involvement that should be included in the differential diagnosis. CNS recurrence of the underlying hematologic disease must be ruled out in patients at high risk for relapse. Overall, clinical manifestations often may be nonspecific and misleading. Assigning the correct diagnosis may be challenging for well-trained clinicians as well, and any significant delay may cause irreversible consequences. Neurologic consultation may be helpful for complicated clinical cases. Awareness of the several neurologic complications is of paramount importance to improve clinical outcomes.

DRUG-RELATED TOXICITY

Calcineurin-inhibitors (CNIs), cyclosporine-A (CsA), and tacrolimus (TaC), cytotoxic agents used in conditioning regimens, and antimetabolites are among the most frequent causes of drug toxicity (Table 3). Antibiotics used for either prophylaxis or treatment of infections also may be involved. Most importantly, drug–drug interactions may play a pivotal role in a very complex scenario in which several drugs with potentially different neurotoxicities—such as immunosuppressors, antibiotics, cytotoxic agents, and monoclonal antibodies—are administered simultaneously.

Financial disclosure: See Acknowledgments on page 395.

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http://dx.doi.org/10.1016/j.bbmt.2016.12.632
1083-8791/

Table 1
Categories of CNS Complications

Category	Causative Agents
Drug-related	Calcineurin inhibitors
	Metothrexate
	Cytotoxic agents
	Monoclonal antibodies
	Antibiotics
Metabolic	Hepatic encephalopathy
	Uremic encephalopathy
Infectious	Bacteria
	Viruses
	Fungi
	Protozoa
Cerebrovascular	Hemorrhage
	Ischemic stroke
Immune-mediated	Myositis
	Myasthenia gravis
	Demyelinating diseases
	CNS cGVHD
	CRS

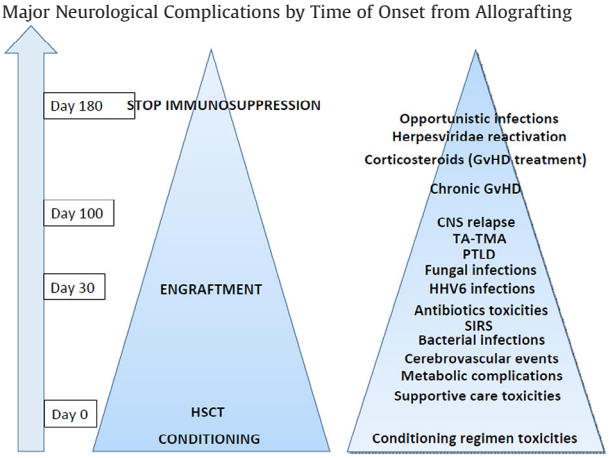
CNS indicates central nervous system; cGVHD, chronic graft versus-host disease; CRS: cytokine release syndrome.

Calcineurin Inhibitors—Cyclosporine and Tacrolimus

CsA and TaC are molecules with marked immunosuppressive properties that are widely used to prevent organ rejection in solid organ transplantation and as prophylaxis/treatment of GVHD in HSCT. Second only to their renal side effects, neurologic complications are reported in 25% to 59% of HSCT recipients [7]. Both the CNS and peripheral nervous system can be affected, with effects ranging from essential tremors and headaches to seizures and serious encephalopathy. Genetic polymorphisms in CYP3A5 and P-glycoprotein encoded by the *ABCB1* gene appear to influence CNI neurotoxicity [8]. Neurotoxic effects are more frequent with elevated serum levels, but can occur at therapeutical serum concentrations as well. Clear insights into the pathophysiology of CNI-related neurotoxicity are lacking. Previous work identified a direct neurotoxic effect of CsA, independent of arterial blood pressure or renal function variations, with neuronal apoptosis and selective oligodendrocyte death [9]. Arterial hypertension and electrolyte imbalances, including hypomagnesemia, hyponatremia/hypernatremia, or altered lipid metabolism, are other putative factors in CNI toxicity [10-12]. Damage to the vascular endothelium mediated by endothelins, implicated in cerebral vasospasm, is a well-recognized detrimental effect of CNIs [13]. One peculiarity is that CsA induces neuroprotection from ischemia/reperfusion brain injury in animal models [14]. The delicate balance between neurotoxicity and protection appears to be mediated by the mitochondrial metabolism in several normoxic/hypoxic brain metabolic conditions [15].

The clinical picture of CNI-induced neurotoxicity includes seizures, mainly single and generalized, sometimes with transient postseizure deficits, such as cortical blindness or behavioral abnormalities, ataxia, aphasia, disorientation, confusion, lethargy, asterexis, and altered visual perception, including hallucinations. In some 6% to 9% of HSCT recipients, CNIs may induce posterior reversible encephalopathy syndrome (PRES), a clinical neuroradiologic entity described in the mid-1990s and consisting of a typical, albeit nonspecific, magnetic resonance imaging (MRI) pattern of multifocal areas of signal hyperintensity in T2-weighted sequences, most often in the white matter of occipital lobes and occasional involvement of other sites, such as the cerebellum, brain stem, or basal ganglia [16]. Most importantly, if recognized early, this clinical syndrome, often preceded by seizures and characterized by headache, lethargy, and confusion as well as altered visual perception, is a reversible condition after CNI suspension. Normal clinical conditions and brain imaging may be restored in few weeks, although some long-term resolutions have been reported [17]. Incomplete recovery from PRES also has been described, especially if the clinical syndrome is not promptly recognized and treated. Patients who develop PRES within day +100 after HSCT appear to have shorter overall survival [18]. Substitution of CsA with TaC might be helpful despite the drugs' similar mechanism of action [19]. The estimated incidence of TaC neurotoxicity is around 30%, mostly consisting of mild symptoms, such as fine tremor of the upper extremities (most common effect), insomnia, headache, dysesthesia, and photophobia. Major neurologic side effects were reported in a minority of patients, with both early and late onset of symptoms after transplantation. These included severe multifocal demyelinating sensorimotor polyneuropathy, akinetic mutism, extrapyramidal syndrome with pseudobulbar dysarthria and opisthotonus with severe rigidity, psychosis with maniacal episodes, and PRES [20,21].

Table 2
Major Neurological Complications by Time of Onset from Allografting



HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; CNS, central nervous system; TA-TMA, transplantation-associated thrombotic microangiopathy; PTLD, post-transplantation lymphoproliferative disorders; HHV-6, human herpesvirus 6; SIRS, systemic inflammatory response syndrome.

Metothrexate

Low-dose i.v. methotrexate used for GVHD prophylaxis causes only occasional minor neurotoxic events, such as headache, dizziness, and, very rarely, seizures. Although extremely rare, diffuse necrotizing leukoencephalopathy, typical of high-dose i.v. therapy [22] for malignant lymphomas or osteogenic sarcomas, also has been reported after low-dose oral methotrexate therapy [23].

Cytotoxic Agents

Busulfan is associated with neurotoxicity and risk of seizures in both adult and pediatric patients. The estimated incidence of neurotoxicity is approximately 10% in the absence

Table 3
Neurotoxicity of Immunosuppressive Agents and Cytotoxic Drugs Used in Hematopoietic Stem Cell Transplantation

Drug	Most common symptoms	References
Cyclosporine A	Tremor, confusion; PRES; cortical blindness; ataxia	Reece et al., 1991 [7] Bartynski, 2008 [16] Ayas et al., 2008 [19]
Tacrolimus	Tremor, confusion; PRES; cortical blindness; ataxia	Eidelman et al., 1991 [20] Hammerstrom et al., 2013 [21]
Metothrexate	Leukoencephalopathy	Bhojwani et al., 2014 [22] Paudyal et al., 2010 [23]
Busulfan	Seizures	Caselli et al., 2014 [24] Eberly et al., 2008 [25]
Fludarabine	Severe encephalopathy	Beitinjaneh et al., 2011 [26]
Alemtuzumab	PML; demyelinating syndrome	Isidoro et al., 2014 [36]
Rituximab	PML	Carson et al., 2009 [37]
Sorafenib	PRES	Tavil et al., 2016 [39]
Blinatuomab	Encephalopathy; aphasia, ataxia; tremor, confusion	Goebeler et al., 2016 [38]
Ifosfamide	Severe encephalopathy	Ajithkumar et al., 2007 [27] Pelgrims et al., 2000 [28]
Carmustine	Facial flushing; paresthesias; severe encephalopathy	Woo et al., 1997 [29] Jagannath et al., 1989 [30]
Cytarabine	Cerebellar toxicity; seizures; lymphocytic meningitis	Patel et al., 2012 [31] Vaughn et al., 1993 [32]
Etoposide	Peripheral neuropathy; PRES	Imrie et al., 1994 [33] Khanal et al., 2013 [34]

PRES indicates posterior reversible encephalopathy syndrome; PML, progressive multifocal leukoencephalopathy.

of adequate pharmacologic prophylaxis, and only 1.3% with appropriate prophylaxis [24]. Busulfan crosses the blood-brain barrier and may build up in potentially high concentrations in the cerebrospinal fluid (CSF). It probably causes direct neurotoxicity and decreases the threshold level for seizures. Preventive treatment with phenobarbital sodium, benzodiazepines, or phenytoin is recommended [25].

Fludarabine is a purine analog associated with the development of dose-related neurotoxicity. Its manifestations may be similar to those of PRES, referred to as an acute toxic leukoencephalopathy. Cognitive impairment associated with visual and sensitive defects is the hallmark of this clinical syndrome. MRI of the brain may show bilateral signal alterations in the deep white matter, rather distinct from the MRI findings seen in PRES [26]. The neurotoxicity of other cytotoxic compounds more commonly used in the autologous HSCT setting is reported in Table 3 [27-34].

Monoclonal Antibodies and Tyrosine Kinase Inhibitors

Monoclonal antibodies have been associated with an elevated risk of progressive multifocal leukoencephalopathy (PML), a demyelinating CNS disease most commonly caused by John Cunningham virus (JCV) infection/reactivation [35]. Alemtuzumab, an anti-CD52 monoclonal antibody, a strong lymphocyte-depleting agent [36], and the chimeric monoclonal antibody anti-CD20 rituximab, have been associated with PML. The pathogenesis likely relies on a perturbation of the immune system with as-yet unknown mechanisms. Clinical symptoms include dysesthesia, ataxia, aphasia, and cognitive decline, with onset at a median of 6 months after the last dose. Clinical progression is very rapid, with a fatal course in nearly all cases [37].

Recently, monoclonal antibodies and targeted therapies, such as tyrosine kinase inhibitors (TKIs), have been combined with allografting either as "bridge" to HSCT, to reduce the tumor burden, or after HSCT, to allow for long-term disease control. Potential neurologic toxicities associated with these agents should be taken into account. Blinatumomab, a bi-specific T cell engager with specificity for both CD19 and CD3, recently used as bridge to transplantation in relapsed/refractory lymphoblastic leukemias, may cause neurotoxicities, such as as encephalopathy, aphasia, hemiparesis, seizures, apraxia, and tremor [38]. Moreover, TKIs are sometimes used before HSCT in Philadelphia chromosome–positive disorders and sorafenib in Flt3-positive acute myelogenous leukemias, although these agents are rarely associated with PRES [39,40].

Antibiotics and Supportive Medications

Neurologic toxicity during prophylaxis and/or treatment of infectious complications has been reported. Aciclovir, adopted for herpes simplex virus (HSV)/varicella-zoster virus (VZV) prophylaxis and treatment, may cause such neurologic complications as encephalopathy and posterior leukoencephalopathy [41]. Amphotericine B therapy for invasive fungal infections has been associated with the rare development of reversible encephalopathy and Parkinson-like syndrome [42], whereas altered visual perception associated with voriconazole is a frequent daily-practice side effect [43]. Cefepime, a fourth-generation cephalosporine, is a broad-spectrum antibacterial agent that plays a putative role in severe encephalopathy, especially during concomitant renal insufficiency [44]. There are several reports on the neurotoxic effects of carbapenemics, particularly imipenem/cilastatin [45]. Oxazolidinones are antibacterial drugs generally reserved for vancomycin-resistant enterococcal infections for which some correlations with neurotoxicity exist, particularly with the peripheral nervous system, acting as a painful peripheral neuropathy inducer with concomitant use of selective serotonin reuptake inhibitors and as an optic neuropathy agent [46]. Metronidazole neurotoxicity includes cerebellar disease, sensorimotor peripheral neuropathy, optic neuropathy, and autonomic dysfunction [47,48]. Neurologic manifestations of quinolone toxicity include seizures, encephalopathy, myoclonus, and toxic psychosis [49]. Finally, attention should be given to the neurodepressive properties of supportive care drugs, such as opioid narcotics, antihistamines, benzodiazepines, and antiemetics, especially when used in combination.

Cognitive Dysfunction Secondary to High-Dose Chemotherapy

Many patients treated with high-dose cytotoxic agents and/or radiotherapy followed by HSCT suffer from cognitive impairment. A prevalence of 20% to 60%, with an estimated 40% in long-term survivors, has been reported [50,51]. High-dose chemotherapy, a total body irradiation–containing conditioning regimen, metabolic impairment, GVHD, and its treatments are recognized as major risk factors; global health and fatigue could play roles as well [52]. The most common symptoms are loss of motor dexterity, verbal recall and fluency, and executive functions. Medications, such as methylphenidate or modafinil, have shown varying degrees of efficacy [53] Rehabilitation strategies are warranted to treat deficits and prevent long-term cognitive impairments [54].

METABOLIC COMPLICATIONS

Multiorgan failure resulting from a variety of clinical conditions may induce CNS failure, mainly as a consequence of systemic inflammatory response [55]. Pharmacologic sedation with major opioids for mucositis-induced pain is quite common in the setting of allografting; however, the wide variations in opioid metabolism and pharmacokinetics among individuals results in frequent overdosing. Intrathecal morphine-induced encephalopathy has been reported as well [56]. Hepatic encephalopathy is not an unusual complication in the context of other life-threatening conditions, such as veno-occlusive disease. Uremic encephalopathy has been associated with CNI nephrotoxicity and thrombotic microangiopathy/hemolytic-uremic syndrome. The clinical syndrome involves depression of the sensorium, from lethargy to coma, without substantial lateralizing signs. Pupillary light reflex and reflexive tracking eye movements are generally preserved, as opposed to what usually occurs in comas from structural damage.

INFECTIOUS COMPLICATIONS

Several pathogens can cause CNS infection. In a large retrospective survey of more than 650 autologous or allogeneic HSCT recipients, cerebral toxoplasmosis was the most common etiology, followed by infection with *Aspergillus* spp. [57]. Other reports have confirmed toxoplasmosis and fungal infections, particularly aspergillosis, as leading causes of CNS infections, with lower rates of infections of bacterial and viral origin [58,59].

Time of onset—early versus late post-HSCT—and the characteristics of neurologic symptoms are relevant for a correct differential diagnosis. Neurologic symptoms may be classified as 3 main syndromes: seizures, focal brain disease, and diffuse processes. Seizures are a common finding in neurologic infections, but are of an extremely nonspecific nature. Focal brain parenchymal disease is most commonly due to hematogenous spreading from sites outside the CNS. Diffuse meningoencephalitis could also present without the classical signs of stiff neck and headache owing to an altered state of consciousness from metabolic alterations or drug toxicities. Disorientation, lethargy, and stupor are all possible clinical manifestations of widespread brain effects and, the involvement of cranial nerves is not infrequent. Diagnostic assessment includes neuroimaging techniques, such as computed tomography (CT) or the more-sensitive MRI [60]; complete CSF analysis for cell counts, glicorachie, and proteinorachie; Gram staining, cultures, and PCR; and even brain biopsy if clinically indicated.

Fungal Infections

Various fungal agents may cause infections, including brain abscesses due to filamentous fungi such as *Aspergillus* and meningitis sustained by *Candida* or, rarely, *Cryptococcus*. *Aspergillus* is the most frequent and could involve a CNS at any point post-transplantation [61]. CNS aspergillosis is usually disseminated from lung or cranial sinuses by secondary vascular dissemination. The clinical presentation is nonspecific and may include altered level of consciousness with either focal signs of neurologic or meningeal irritation. Although rare, mycotic aneurysm rupture in the subarachnoid space also may occur. CT scan of the head, capable of identify the hemorrhagic component of aspergillosis, is preferred over MRI. CNS aspergillosis commonly presents with lesions in cerebral hemispheres, frequently multiple and often associated with edema, mass effect, and areas of ischemia or hemorrhage. Concomitant demonstration of *Aspergillus* in cultures obtained from lung and pleural fluids is highly suggestive of CNS aspergillosis. The detection of galactomannan in CSF by ELISA is a useful diagnostic tool to confirm invasive aspergillosis [62]. Histopathological isolation of *Aspergillus* spp. from brain tissue remains the gold standard diagnostic approach. Voriconazole and liposomal amphotericin are current first-line treatments [63,64], although azole-resistant *Aspergillus* strains remain of concern [65].

In a historical control, the incidence of *Candida* spp. CNS infections was 3% in patients with systemic candidaemia [66] and up to 6% in a post mortem analysis [67], indicating an underestimated incidence. Most reported cases are due to *Candida albicans*, but non-*albicans* species are being increasingly reported [68]. Clinical manifestations include primarily meningitis, with diffuse encephalopathy owing to multiple brain abscesses, ventriculites, and subarachnoid hemorrhage in the rare event of a mycotic aneurysm rupture. Fungemia on blood cultures is present in 70% of patients. The sensitivity of CSF cultures for the diagnosis of *Candida* meningitis is relatively low. A *Candida* antigen mannan/antimannan assay in CSF may be helpful [69]. Polyenes, echinocandines, and fluconazole are the most effective agents, although the response to treatment is unpredictable, and mortality rates remain very high [70].

Mucorales—*Mucor*, *Absidia*, and *Rhizopus*—may cause CNS infections in immunocompromised patients [71]. The infection initially presents with mucous involvement of nasal, oral, or cranial sinuses and spreads rapidly to the orbit or the cranial base. Biopsies of infected lesions are essential for timely treatment and good clinical outcome. Surgical debridement of infected/necrotic tissue is almost mandatory, even though it may be extremely destructive for the patient. The infection is invariably fatal within a few days without prompt, appropriate treatment. Combination therapy with lipid formulations of amphotericin and echinocandins is standard treatment [72].

Cryptococcal CNS infection is typical of HIV-infected patients and presents as subacute or chronic meningitis. It is very rarely reported in HSCT recipients [73]. *Cryptococcus neoformans* has a perivascular tropism with formation of gelatinous microscopic abscesses in the Virchow-Robin spaces. It usually follows a pulmonary route. MRI is the most sensitive imaging technique, although brain scans often appear totally normal. Antigen detection and PCR of body fluids have a sensitivity >90% and are very specific. Polyenes, flucytosine, and fluconazole are the backbone of therapy for cryptococcal meningitis [74].

Histoplasma capsulatum causes systemic infections in endemic areas. It is far more common in patients with HIV and in solid organ transplant recipients compared with HSCT recipients [75]. Long-term lipid formulation amphotericin B-based therapy is mandatory to prevent relapse [76].

Coccidioidal meningitis is another CNS infection of endemic areas of the southwestern United States and northern Mexico [77]. In a recent retrospective analysis of 426 allogeneic HSCTs, the overall incidence of coccidioidomycosis was 2.6%, with only 9% of infected patients having extrapulmonary involvement [78]. Therapy is azole-based with intrathecal polyene injection, but prognosis remains dismal.

Neurotoxoplasmosis

Toxoplasma gondii is an important cause of brain abscess in allogeneic HSCT recipients and was the most frequent pathogen isolated from CNS infections in 2 recent retrospective studies [57,58]. Altered level of consciousness and focal neurologic deficits are frequent at onset. The increase in intracranial pressure due to *T. gondii*'s tropism for the periventricular location often results in obstructive hydrocephalus. Toxoplasmosis presents with multiple abscesses, typically in the white or gray matter of the cerebral hemispheres, associated with ring enhancement on both CT scans and MRI [79]. Detection of toxoplasma-DNA by PCR in CSF is the main diagnostic tool [80]. Stereotactic brain biopsy is required to obtain a histological diagnosis. Trimethoprim-sulphamethoxazole (TMP-SFX) with clindamycin or pyrimethamine is the current therapy of choice. Prevention strategies with antiprotozoal molecules have been recommended [81].

Viral Infections

A retrospective multicenter study of allogeneic HSCT recipients showed an incidence of 1.2% during the first 3 years post-transplantation, with HHV-6 as the most frequent causative agent [82]. Viral encephalitis due to HHV-6 is being increasingly recognized as a CNS pathogen in HSCT recipients [83], with a higher incidence in cord blood transplants [84]. Fever, headache, obtundation, and a typical short-term memory loss are the most common neurologic signs, occurring as early as 2 to 6 weeks post-HSCT. Viral DNA detection by PCR is a sensitive assay for HHV-6 in both blood and CSF samples [85]. MRI commonly reveals bilateral abnormalities in the limbic system. Ganciclovir (GCV) and foscarnet (FOS) are common treatments, although their efficacy does not appear to be optimal. Given the rapidly progressive onset of neurologic symptoms, prompt initiation of antiviral therapy is mandatory.

Cytomegalovirus (CMV) CNS disease is a rare clinical finding and generally occurs late after transplantation, at a median of >4 months. It carries a mortality rate >80% [86]. The increased use of T cell–depleted grafts, the rise of antiviral-resistant CMV strains, and the increasing age of HSCT recipients may contribute to an overall higher incidence of CNS disease [87]. Ventriculoencephalitis with microglial nodules is the classic major expression of CNS infection. PCR analysis of CSF samples, confirmed by culture or brain biopsy, is required for a definitive diagnosis. Treatment is based on a combination of GCV and FOS, although GCV-resistant CMV strains are an emerging concern [88].

VZV typically causes late infections, with a peak occurring in months 4 and 5 post-HSCT. Before the widespread use of antiviral agents, the reported incidence of clinical encephalitis was 4% of all HSCT recipients with active VZV infection [89]. In a recent retrospective single-center study in which routine VZV prophylaxis was not provided, the authors reported a 2-year incidence of VZV reactivation of 20.7% [90]. Overall, the most significant risk factor for VZV CNS disease is chronic GVHD and its treatment [91]. Meningoencephalitis is the main manifestation, with fever, headache, somnolence, and often seizures; however, other symptoms due to spinal cord engagement, such as facial nerve palsy, hearing loss, arm weakness, and neurogenic bladder, may be present as well. Dermatomal zoster can precede the onset of CNS disease. The clinical course is often fatal. High-dose aciclovir is the recommended treatment [92].

HSV1-2 infections are not infrequent in HSCT recipients, although their dissemination to the CNS is not common. They cause encephalitis with or without meningeal involvement. MRI may show alterations of the mesial temporal structures. HSV-PCR on CSF is a highly sensitive diagnostic technique. Therapy consists of high-dose aciclovir; two-thirds of the surviving patients will have long-term neurologic disability despite prompt initiation of therapy [92,93].

PML is a rare demyelinating disease first described in 1958 caused by JCV infection/reactivation and characterized by multifocal demyelinating areas of the brain with progressive neurologic deficits [94]. Recently, one group suggested a role of B-lymphocytes in the development of PML, as a viral reservoir/vector of CNS dissemination [95]. The usual presentation includes a unifocal neurologic syndrome involving the cortex, brain stem, or cerebellum with sparing of optic nerves and spinal cord. Visual deficits, hemiparesis, or frontal lobe dementia with behavioral changes are common clinical symptoms. The median time of symptom onset is usually months after HSCT. Disease progression is subacute. MRI is both sensitive and specific. T2-weighted and FLAIR MRI sequences show hyperintense multifocal asymmetric white matter lesions without mass effect and minimum contrast enhancement after gadolinium injection. PCR on CSF is the most helpful test for noninvasive diagnostic confirmation [96]. No treatment has proven effective, including antivirals, antimalarial drugs such as mefloquine, psychiatric medications, and immune stimulants. Patients who survive the infection often suffer from permanent neurologic deficits.

West Nile virus (WNV), a virus of the family Flaviviridae, may cause potentially lethal neuroinvasive disease in an immunocompromised host, with an estimated higher incidence in HIV patients and in solid organ transplantation recipients rather than HSCT recipients [97]. Although rare, adenovirus infection in HSCT recipients, with fatal meningoencephalitis, also has been reported. Cidofovir or ganciclovir therapy is the treatment of choice [98].

Bacterial Infections

Bacterial infections usually occur concomitantly with systemic infection and neutropenia. They can present as either meningitis or brain abscess. In the former, sensorium alteration is quite common, but classical meningeal signs may be mild or absent owing to an impaired inflammatory response. In the latter, altered consciousness and a rapidly evolving focal neurologic deficit, including hemiparesis, with fever is present in 50% of patients. Meningitis is usually associated with a single organism, whereas brain abscess can be of multimicrobial etiology. Gram-negative rods, as well as gram-positive cocci and anaerobic organisms, may be involved, including *Staphylococcus aureus*, coagulase-negative staphylococci such as *S. epidermidis* or *S. hominis*, and alpha-hemolytic *Streptococcus*, which can complicate i.v. line–associated infections. Enterococci and nonfermenting gram-negative bacilli can reach the CNS through the blood after gastrointestinal translocation. Paranasal or other sinus sites can be another relevant source of bacterial spread to the CNS. Encapsulated bacteria—*Streptococcus pneumoniae*, *Neisseria*

meningitidis, and *Haemophilus influenzae*—may cause meningitis, especially in the context of long-lasting immunosuppression. Vaccination against these agents is mandatory. *Mycobacterium tuberculosis* CNS infection has been reported after HSCT [99]. *Listeria monocytogenes* was historically one of the most common causes of bacterial CNS infection, but its incidence has declined with improved supportive care and TMP-SMX prophylaxis. Its common clinical manifestation is a subacute purulent meningitis occurring almost invariably during bacteremia. Concomitant CSF and blood cultures are of paramount importance to establish the correct diagnosis. Real-time PCR is currently standard diagnostic practice. A combination of ampicillin and gentamicin is the therapy of choice [100].

Nocardia is a gram-positive bacterium that may cause brain abscess as a consequence of hematogenous dissemination, commonly from primary pulmonary infection. Lymphopenia and steroid therapy represent major risk factors. Clinical manifestations may appear several months after HSCT and may include focal neurologic symptoms, depending on the site of the abscess. Imaging studies reveal multiple or multiloculated abscesses with ring enhancement after contrast. TMP-SMX is the treatment of choice along with carbapenemics, aminoglycosides, and linezolid [101].

CEREBROVASCULAR DISEASE

Hemorrhagic or thrombotic complications are potentially lethal events. Subdural hematoma is one of the most frequent complications. An incidence of 2.6% was reported in a retrospective analysis of 657 recipients of either autologous or allogeneic HSCT [102]. Refractoriness to platelet transfusions was correlated with an increased risk of bleeding [103]. Other factors, such as arterial hypertension, fibrinogen serum level, and grade III-IV acute GVHD, have been shown to play roles in cerebrovascular hemorrhagic events [104]. The clinical picture is characterized by headache and worsening sensorium without lateralizing signs. Diagnosis sometimes may be challenging in sedated patients and patients with metabolic-driven encephalopathy. CT scans generally show a hyperintense signal of blood at least 12 hours before MRI. Nonetheless, 20% to 25% of patients have a negative CT scan. Neurosurgery is reccomended if clinically possible, especially in those patients who present with progressive neurologic deterioration or voluminous lesions [105]. Conservative strategies may be considered in noncomplicated cases. Parenchymal hemorrhages are most frequently associated with long-lasting severe thrombocytopenia and are almost invariably lethal [106]. An abrupt onset of neurologic deficits, quickly followed by depressed sensorium and brain stem signs from transtentorial herniation, is typical of fatal large intracranial hemorrhages. The only treatment is surgical, but its feasibility is very limited. In contrast, subarachnoid hemorrhage is not frequent, and its severity depends on its extension, localization, and causative trigger. Cerebrovascular thrombotic events may be associated with a hypercoagulative state or with thromboembolism from endocarditis or atrial fibrillation. A recent study of 431 allogeneic HSCT recipients found that clinically significant cerebral bleeding was more common than symptomatic thrombotic events, and that the cumulative incidences of venous and arterial thrombosis at 14 years were 11.8% and 4.1%, respectively [107]. Chronic GVHD and steroid treatment are major risk factors for thrombotic events [108]. These events are often a complication of underlying active infections, as reported in 36 allogeneic HSCT recipients who experienced cerebral stroke, in whom one-third of the events were infection-triggered, mostly of fungal origin [109].

IMMUNE-MEDIATED DISORDERS

Three main immune-mediated disorders have been described in allogeneic HSCT recipients: myositis, myasthenia gravis (MG), and Guillain-Barrè–like demyelinating polyneuropathy. CNS manifestations of chronic GVHD also have been reported. Cytokine release syndrome (CRS) is included as well.

Myositis

Myositis is a rare neuromuscular complication associated with chronic GVHD, with an estimated incidence of 2% to 3% [110]. Moderate to severe proximal muscle weakness is the hallmark of myositis [111]. Elevated levels of creatine-phosphokinase are closely correlated with this complication's clinical course. Needle electromyography often shows a typical myopathic pattern. To confirm the diagnosis, muscle biopsies are useful to demonstrate segmental muscle fiber necrosis and regeneration, mononuclear cell inflammation, and a lymphocytic infiltration of donor origin. MRI is commonly used to establish the diagnosis and monitor disease activity. Corticosteroids are the treatment of choice, with responses expected after a few days to 4 to 6 weeks [112].

Myasthenia Gravis (MG)

This immune-mediated disorder involves the neuromuscular junctions, with an incidence lower than 1%. It is usually diagnosed after the onset of chronic GVHD, generally several months after HSCT [113]. Fatiguable muscle weakness, including ptosis, dysphagia, dysarthria, diplopia, and facial, limb, or axial weakness, are the main symptoms. No relationship with thymoma has been observed in allogeneic HSCT recipients, unlike in idiopathic MG, where the association with thymic neoplasms may be as high as 15% [114]. Serum anti-acetylcholine receptor antibodies can be detected in a proportion of patients; however, these autoantibodies are present in up to 40% of allogeneic HSCT recipients without disease, and their diagnostic reliability is questionable [115]. Electrophysiological testing showing a progressive decrease in the muscle action potential supports a definitive diagnosis. Treatment consists of oral cholinesterase inhibitors and steroids or other immunosuppressive agents for severe clinical symptoms.

Acute Immune-Mediated Neuropathies

Immune-mediated neuropathies, including Guillain-Barrè-like syndrome (GBS), have an estimated incidence of 1% [116,117]. They usually develop within the first 3 months after HSCT. GBS can be present with or without acute GVHD. Characterized by a progressive symmetrical ascending motor weakness, hyporeflexia, and numbness, GBS is accompanied by respiratory insufficiency that may require artificial ventilation in up to 25% of cases. GBS can be preceded by infection, as in its idiopathic form. Electrophysiological demonstration of slowed or blocked nerve conduction is essential for diagnosis. Plasma exchange or i.v. polyclonal gamma globulin therapy is the treatment of choice [118]. Rituximab therapy has been used in patients with unresponsive disease [119]. Worsening clinical condition has been reported in allogeneic HSCT recipients with preexisting GBS treated with a total body irradiation–containing conditioning regimen [120].

CNS Manifestations of Chronic GVHD

The potential for neurologic manifestations of chronic GVHD has been reported [121,122]. Three major clinical manifestations have been described: cerebrovascular disease, demyelinating processes, and immune-mediated encephalitis. The first of these manifestations is characterized by vasculitis of small- to medium-sized arterial vessels of meninges and cerebral parenchyma, marked by inflammatory infiltrates of monocytes and $CD3^+CD8^+$ T cells of donor origin. Diseases of small vessels are accompanied by rather nonspecific symptoms. MRI frequently shows multifocal signal changes in the white matter, along with ischemic lesions and minute hemorrhages [123]. In contrast, diseases of medium to large vessels present with hemiparesis or other focal neurologic signs in cases of ischemic/hemorrhagic stroke. Definitive diagnosis requires brain biopsy, although the sensitivity is low. Treatment of biopsy-proven cerebral vasculitis consists of corticosteroids, usually in combination with cyclophosphamide, for 3 to 6 months until the induction of remission. Demyelinating disease has been observed in the optic nerve, cerebral white matter, and spinal cord. A relapsing-remitting course, as seen in multiple sclerosis, is usual [124]. Diagnosis relies on MRI demonstration of white matter lesions and inflammatory signs in the CSF. Corticosteroid pulses are the mainstay of treatment.

Finally, so-called immune-mediated encephalitis includes a group of pathological entities caused by CNS infiltration of immune cells that cause functional neurologic deficits. Differential diagnosis with infectious encephalitis requires careful analysis of CSF cell counts and serology, culture, and PCR results.

CRS

CRS is a potentially life-threatening complication usually observed after haploidentical and, more recently, adoptive T cell therapies for cancer, such as the infusion of chimeric antigen receptor (CAR) T cells [125]. CRS is a systemic inflammatory response characterized by high levels of IL-6, IL-2, IFN-γ, and tumor necrosis factor. If not managed promptly and properly, CRS can result in multiorgan failure [126]. An incidence of 50% has been reported after CAR T cell infusion [127]. CNS involvement is rather similar to that reported with the monoclonal antibody blinatumomab and includes both encephalopathy and cranial nerve palsies, ataxia, aphasia, and hemiparesis. Airway protection requiring intubation is required in some cases. Patients receiving anti-CD19 CAR T cells apparently are more prone to neurotoxicity [128].

ALLOGENEIC HSCT-ASSOCIATED THROMBOTIC MICROANGIOPATHY

Transplantation-associated thrombotic microangiopathy (TA-TMA) is a pathological entity of endothelial damage and arteriolar thrombosis, distinct from classical hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura, with an estimated incidence of 10% to 35% [129]. Pathological hallmarks included generalized endothelial dysfunction, intravascular platelet activation, and formation of thrombi within the microcirculation. Microangiopathic hemolytic anemia with de novo thrombocytopenia, elevated lactate dehydrogenase, and >5% schistocytes in peripheral blood, in the absence of coagulation abnormalities, are typical laboratory findings. Clinical signs/symptoms depend on the extension of organ involvement, including renal, gastrointestinal tract, liver, lung, and CNS. Unlike in thrombotic thrombocytopenic purpura, ADAMTS-13 levels are normal or only slightly reduced [130]. Activation of the complement system, with increased C5b-9 serum concentration, plays a relevant role in the induction of primary endothelial damage. Alterations in the genetic expression of proteins involved in the alternative coagulation pathway have been reported as well [131]. Neurologic deficits may be present in 30% of patients with TA-TMA [132]. Imaging studies suggestive of PRES are present in only a minority of cases. No standard treatment exists; however, new insights into the pathogenesis of TA-TMA have drawn attention to antibody-mediated complement cascade blockers and endothelial-protective agents [133]. Eculizumab, a terminal complement blocker, appears to be the most interesting new agent, with encouraging response rates [134]. In a cohort of 30 patients with high-risk TA-TMA, Jodele et al. [121] reported a 1-year overall survival of 62% in eculizumab-treated patients, compared with 9% in patients who received other treatments. Defibrotide, an endothelial-protective drug approved for the treatment of sinusoidal obstructive syndrome and capable of reducing the procoagulant activity and increasing the fibrinolytic properties of endothelial cells, has emerged as a potentially effective agent in TA-TMA treatment, with a 55% response rate reported in 551 patients [129]. The monoclonal antibody anti-CD20 rituximab has shown efficacy in this context as well [135]. The discontinuation of CNI therapy at the onset of TA-TMA may be beneficial.

POST-TRANSPLANTATION LYMPHOPROLIFERATIVE DISORDERS AND DISEASE RECURRENCE

Post-transplantation lymphoproliferative disorders (PTLDs) may involve the CNS as a systemic extranodal illness or, rarely, as a single manifestation. Most PTLDs are associated with Epstein-Barr virus (EBV) reactivation. PTLDs are classified as 4 clinicopathological entities with a highly variable clinical spectrum, ranging from self-limited proliferation of lymphoid cells to rapidly fatal disease [136]. Isolated CNS PTLDs present with nonspecific clinical symptoms. Multiple bilateral hemispheric lesions with involvement of the subcortical white matter and basal ganglia are the typical imaging findings. Exclusion of infectious diseases, particularly of CNS nocardiosis, CNS toxoplasmosis, and viral encephalitis, is mandatory. Reduction of immunosuppression to restore host immune competence is the first-line treatment of choice in nonaggressive disease, with rituximab-based chemotherapy for all other cases [137]. Intraventricular rituximab injection has been used in patients with lymphomatous meningitis [138]. Response rates are quite encouraging, but incomplete T cell immune recovery determines a high risk of disease recurrence [139]. Importantly, hematologic malignancies with primary CNS and/or craniofacial/paravertebral involvement at diagnosis increase the risk of both disease relapse after HSCT and nonspecific CNS complications. Prophylactic intrathecal therapy is mandatory in all patients at high risk for CNS localization post-HSCT, especially in lymphoblastic leukemia, acute myelogenous leukemia with CNS involvement, CNS plasmocytomas, aggressive non-Hodgkin lymphomas with CNS, and parasinus, intraocular, spinal, or testicular localizations at diagnosis [140].

DIAGNOSTIC ALGORITHM

Given that a large proportion of neurologic complications are attributable to metabolic and drug toxicities, a careful review of the medication history is mandatory. Furthermore, the time of onset of neurologic signs and/or symptoms after HSCT may be very helpful. Based on physical examination findings, 2 major neurologic syndromes may be defined:

one patient group with transient generalized signs and/or symptoms (eg, seizures, altered consciousness) and another group with focal signs suggesting a localized lesion (eg, mass lesion of any origin, stroke). Neuroimaging with CT scans and MRI plays an important role, especially for ruling out cerebrovascular events, parenchymal infiltrates, PRES, or early disease relapse. Lumbar punctures allow CSF chemical and physical analyses and cell counts, which are of great value for diagnosing infectious diseases or early leukemic infiltration. Brain biopsy is very rarely performed because of its invasive nature. It is clinically indicated for focal lesions where other, less invasive procedures have not been useful. Among others, diagnosis of complications such as opportunistic infections, malignancies, PML, and vasculitis may require histology studies. Nerve conduction studies should be considered when polyneuropathies are observed or neuromuscular abnormalities are suspected. Electroencephalography may be very useful in critically ill patients with altered consciousness or seizures. Finally, the ultimate opinion of a consultant neurologist is highly recommended and should be considered mandatory in complex scenarios.

CONCLUSION

Neurologic complications after HSCT are not uncommon, and their etiology is multifactorial. The toxic effects of drugs used in conditioning, immunosuppressive agents, and antibiotics for prophylaxis/treatment of infections account for most of these complications in the early post-transplantation period. Recently described CNS manifestations of chronic GVHD and immune-mediated disorders, including neuromuscular and peripheral nerve diseases, are infrequent but difficult to manage. Prompt diagnosis and timely treatment are extremely important to avoid long-term neurologic disabilities and improve clinical outcomes.

ACKNOWLEDGMENTS

Conflict of Interest Statement: There are no conflicts of interest to report.

REFERENCES

1. Passweg JR, Baldomero H, Peters C, et al. Hematopoietic SCT in Europe: data and trends in 2012 with special consideration of pediatric transplantation. *Bone Marrow Transplant* 2014;49:744-750.
2. Tauro S, Craddock C, Peggs K, et al. Allogeneic stem-cell transplantation using a reduced-intensity conditioning regimen has the capacity to produce durable remissions and long-term disease-free survival in patients with high-risk acute myeloid leukemia and myelodysplasia. *J Clin Oncol* 2005;23:9387-9393.
3. Ustun C, Lazarus HM, Weisdorf D. To transplant or not: a dilemma for treatment of elderly AML patients in the twenty-first century. *Bone Marrow Transplant* 2013;48:1497-1505.
4. Barba P, Piñana JL, Valcárcel D, et al. Early and late neurological complications after reduced-intensity conditioning allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 2009;15:1439-1446.
5. Bleggi-Torres LF, de Medeiros BC, Werner B, et al. Neuropathological findings after bone marrow transplantation: an autopsy study of 180 cases. *Bone Marrow Transplant* 2000;25:301-307.
6. Siegal D, Keller A, Xu W, et al. Central nervous system complications after allogeneic hematopoietic stem cell transplantation: incidence, manifestations, and clinical significance. *Biol Blood Marrow Transplant* 2007;13:1369-1379.
7. Reece DE, Frei-Lahr DA, Shepherd JD, et al. Neurologic complications in allogeneic bone marrow transplant patients receiving cyclosporine. *Bone Marrow Transplant* 1991;8:393-401.
8. Yanagimachi M, Naruto T, Tanoshima R, et al. Influence of CYP3A5 and ABCB1 gene polymorphisms on calcineurin inhibitor-related neurotoxicity after hematopoietic stem cell transplantation. *Clin Transplant* 2010;24:855-861.
9. McDonald JW, Goldberg MP, Gwag BJ, Chi SI, Choi D. Cyclosporine induces neuronal apoptosis and selective oligodendrocyte death in cortical cultures. *Ann Neurol* 1996;40:750-758.
10. Morgan BJ, Lyson T, Scherrer U, Victor R.G. Cyclosporine causes sympathetically mediated elevations in arterial pressure in rats. *Hypertension* 1991;18:458-466.
11. Thompson CB, June CH, Sullivan KM, Thomas ED. Association between cyclosporin neurotoxicity and hypomagnesaemia. *Lancet* 1984;2:1116-1120.
12. de Groen PC, Aksamit AJ, Rakela J, Forbes G, Krom R. Central nervous system toxicity after liver transplantation: the role of cyclosporine and cholesterol. *N Engl J Med* 1987;317:861-866.
13. Cauduro RL, Costa C, Lhulier F, et al. Endothelin-1 plasma levels and hypertension in cyclosporine-treated renal transplant patients. *Clin Transplant* 2005;19:470-474.
14. Folbergrová J, Li PA, Uchino H, Smith ML, Siesjö BK. Changes in the bioenergetic state of rat hippocampus during 2.5 min of ischemia, and prevention of cell damage by cyclosporin A in hyperglycemic subjects. *Exp Brain Res* 1997;114:44-50.
15. Bernardi P, Vassanelli S, Veronese P, Colonna R, Szabo I, Zoratti M. Modulation of the mitochondrial permeability transition pore: effect of protons and divalent cations. *J Biol Chem* 1992;267:2934-2939.
16. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. *AJNR Am J Neuroradiol* 2008;29:1036-1042.
17. Singh N, Bonham A, Fukui M. Immunosuppressive-associated leukoencephalopathy in organ transplant recipients. *Transplantation* 2000;69:467-472.
18. Lucchini G, Grioni D, Colombini A, et al. Encephalopathy syndrome in children with hemato-oncological disorders is not always posterior and reversible. *Pediatr Blood Cancer* 2008;51:629-633.
19. Ayas M, Al-Jefri A, Al-Seraihi A. In cyclosporine-induced neurotoxicity, is tacrolimus an appropriate substitute or is it out of the frying pan and into the fire? *Pediatr Blood Cancer* 2008;50:426.
20. Eidelman BH, Abu-Elmagd K, Wilson J, et al. Neurologic complications of FK 506. *Transplant Proc* 1991;23:3175-3178.
21. Hammerstrom AE, Howell J, Gulbis A, Rondon G, Champlin RE, Popat U. Tacrolimus-associated posterior reversible encephalopathy syndrome in hematopoietic allogeneic stem cell transplantation. *Am J Hematol* 2013;88:301-305.
22. Bhojwani D, Sabin ND, Pei D, et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. *J Clin Oncol* 2014;32:949-959.
23. Paudyal B, Viets R, Skliut M. A case of low-dose oral methotrexate-induced reversible neurotoxicity. *AJNR Am J Neuroradiol* 2010;31:E77.
24. Caselli D, Rosati A, Faraci M, et al. Risk of seizures in children receiving busulphan-containing regimens for stem cell transplantation. *Biol Blood Marrow Transplant* 2014;20:282-285.
25. Eberly AL, Anderson GD, Bubalo JS, McCune JS. Optimal prevention of seizures induced by high-dose busulfan. *Pharmacotherapy* 2008;28:1502-1510.
26. Beitinjaneh A, McKinney AM, Cao Q, Weisdorf DJ. Toxic leukoencephalopathy following fludarabine-associated hematopoietic cell transplantation. *Biol Blood Marrow Transpl* 2011;17:300-308.
27. Ajithkumar T, Parkinson C, Shamshad F, et al. Ifosfamide encephalopathy. *Clin Oncol (R Coll Radiol)*. 2007;19:108-114.
28. Pelgrims J, De Vos F, Van den Brande J, et al. Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. *Brit J Cancer*. 2000;82:291-294.
29. Woo MH, Ippoliti C, Bruton J, et al. Headache, circumoral paresthesia, and facial flushing associated with high-dose carmustine infusion. *BMT*. 1997;19:845-847.
30. Jagannath S, Armitage JO, Dicke KA, et al. Prognostic factors for response and survival after high-dose cyclophosphamide, carmustine, and etoposide with autologous bone marrow transplantation for relapsed Hodgkin's disease. *JCO*. 1989;7:179-185.
31. Patel RS, Rachamalla M, Chary NR, et al. Cytarabine induced cerebellar neuronal damage in juvenile rat: correlating neurobehavioral performance with cellular and genetic alterations. *Toxicology*. 2012;293:41-52.
32. Vaughn DJ, Jarvik JG, Hackney D, et al. High-dose cytarabine neurotoxicity: MR findings during the acute phase. *AJNR Am J Neuroradiol*. 1993;14:1014-1016.
33. Imrie KR, Couture F, Turner CC, et al. Peripheral neuropathy following high-dose etoposide and autologous bone marrow transplantation. *BMT*. 1994;13:77-79.
34. Khanal P, Awan F, Nguyen V. Etoposide-induced posterior reversible encephalopathy syndrome. *Ann Hematol*. 2013;92:561-562.
35. Takao M. Targeted therapy and progressive multifocal leukoencephalopathy (PML): PML in the era of monoclonal antibody therapies]. *Brain Nerve* 2013;65:1363-1374 [in Dutch].
36. Isidoro L, Pires P, Rito L, Cordeiro G. Progressive multifocal leukoencephalopathy in a patient with chronic lymphocytic leukaemia treated with alemtuzumab. *BMJ Case Rep* 2014;2014. doi: 10.1136/bcr-2013-201781.
37. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients:

a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood* 2009;113:4834-4840.
38. Goebeler ME, Knop S, Viardot A, et al. Bispecific T-cell engager (BiTE) antibody construct blinatumomab for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma: final results from a phase I study. *J Clin Oncol* 2016;34:1104-1111.
39. Tavil B, Isgandarova F, Bayhan T, et al. Sorafenib-induced posterior reversible encephalopathy syndrome in a child with FLT3-ITD-positive acute myeloid leukemia. *J Pediatr Hematol Oncol* 2016;38:240-242.
40. Przybylyski A, Esper P. Early recognition and management of posterior reversible encephalopathy syndrome: a newly recognized complication in patients receiving tyrosine kinase inhibitors. *Clin J Oncol Nurs* 2016;20:305-308.
41. Mahad DJ, Helldén A, Jarvis J, Chinnery PF, Mitra D, Gholkar A. Aciclovir-induced posterior leucoencephalopathy. *J Neurol Neurosurg Psychiatry* 2005;76:1308-1309.
42. Kulkantrakorn K, Selhorst JB, Petruska PJ. Cytosine arabinoside and amphotericin B-induced parkinsonism. *Ann Neurol* 1996;39:413-414.
43. Zonios DI, Gea-Banacloche J, Childs R, Bennett JE. Hallucinations during voriconazole therapy. *Clin Infect Dis* 2008;47:e7-10.
44. Fugate JE, Kalimullah EA, Hocker SE, Clark SL, Wijdicks EF, Rabinstein AA. Cefepime neurotoxicity in the intensive care unit: a cause of severe, underappreciated encephalopathy. *Crit Care* 2013;17:R264.
45. Norrby SR. Neurotoxicity of carbapenem antibiotics: consequences for their use in bacterial meningitis. *J Antimicrob Chemother* 2000;45:5-7.
46. Fletcher J, Aykroyd LE, Feucht EC, Curtis JM. Early-onset probable linezolid-induced encephalopathy. *J Neurol* 2010;257:433-435.
47. Patel K, Green-Hopkins I, Lu S, Tunkel AR. Cerebellar ataxia following prolonged use of metronidazole: case report and literature review. *Int J Infect Dis* 2008;12:e111-114.
48. Hobson-Webb LD, Roach ES, Donofrio PD. Metronidazole: newly recognized cause of autonomic neuropathy. *J Child Neurol* 2006;21:429-431.
49. Isaacson SH, Carr J, Rowan AJ. Ciprofloxacin-induced complex partial status epilepticus manifesting as an acute confusional state. *Neurology* 1993;43:1619-1621.
50. Syrjala KL, Artherholt SB, Kurland BF, et al. Prospective neurocognitive function over 5 years after allogeneic hematopoietic cell transplantation for cancer survivors compared with matched controls at 5 years. *J Clin Oncol* 2011;29:2397-2404.
51. Harder H, Van Gool AR, Duivenvoorden HJ, et al. Case-referent comparison of cognitive functions in patients receiving haematopoietic stem-cell transplantation for haematological malignancies: two-year follow-up results. *Eur J Cancer* 2007;43:2052-2059.
52. Sostak P, Padovan CS, Yousry TA, et al. Prospective evaluation of neurological complications after allogeneic bone marrow transplantation. *Neurology* 2003;60:842-848.
53. Lundorff LE, Jønsson BH, Sjøgren P. Modafinil for attentional and psychomotor dysfunction in advanced cancer: a double-blind, randomised, cross-over trial. *Palliat Med* 2009;23:731-738.
54. Ferguson RJ, Ahles TA, Saykin AJ, et al. Cognitive-behavioral management of chemotherapy-related cognitive change. *Psychooncology* 2007;16:772-777.
55. Sonneville R, Verdonk F, Rauturier C, et al. Understanding brain dysfunction in sepsis. *Ann Intensive Care* 2013;3:15.
56. Kakinohana M, Fuchigami T, Nakamura S, Sasara T, Kawabata T, Sugahara K. Intrathecal administration of morphine, but not small doses, induced spastic paraparesis after a noninjurious interval of aortic occlusion in rats. *Anesth Analg* 2003;96:769-775.
57. Maschke M, Dietrich U, Prumbaum M, et al. Opportunistic CNS infection after bone marrow transplantation. *Bone Marrow Transplant* 1999;23:1167-1176.
58. Denier C, Bourhis JH, Lacroix C, et al. Spectrum and prognosis of neurologic complications after hematopoietic transplantation. *Neurology* 2006;67:1990-1997.
59. Hagensee ME, Bauwens JE, Kjos B, Bowden RA. Brain abscess following marrow transplantation: experience at the Fred Hutchinson Cancer Research Center, 1984-1992. *Clin Infect Dis* 1994;19:402-408.
60. Coley SC, Jäger HR, Szydlo RM, Goldman JM. CT and MRI manifestations of central nervous system infection following allogeneic bone marrow transplantation. *Clin Radiol* 1999;54:390-397.
61. Jantunen E, Volin L, Salonen O, et al. Central nervous system aspergillosis in allogeneic stem cell transplant recipients. *Bone Marrow Transplant* 2003;31:191-196.
62. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. *Clin Inf Dis* 2006;42:1417-1427.
63. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;347:408-415.
64. Schwartz S, Ruhnke M, Ribaud P, et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. *Blood* 2005;106:2641-2645.
65. Howard SJ, Cerar D, Anderson MJ, et al. Frequency and evolution of azole resistance in *Aspergillus fumigatus* associated with treatment failure. *Emerg Infect Dis* 2009;15:1068-1076.
66. Verfaillie C, Weisdorf D, Haake R, Hostetter M, Ramsay NK, McGlave P. *Candida* infections in bone marrow transplant recipients. *Bone Marrow Transplant* 1991;8:177-184.
67. Mattiuzzi G, Giles FJ. Management of intracranial fungal infections in patients with haematological malignancies. *Br J Haematol* 2005;131:287-300.
68. Pfaller MA, Jones RN, Messer SA, Edmond P, Wenzel RP, for the SCOPE Participant Group. National surveillance of nosocomial blood stream infection due to species of *Candida* other than *Candida albicans*: Frequency of occurrence and antifungal susceptibility in the SCOPE program. *Diagn Microbiol Infect Dis* 1998;30:121-129.
69. Biesbroek JM, Verduyn Lunel FM, Kragt JG, Amelink GJ, Fijns CJM. Culture-negative *Candida* meningitis diagnosed by detection of *Candida* mannan antigen in CSF. *Neurology* 2013;81:1555-1556.
70. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016;62:e1-50.
71. Binder U, Maurer E, Lass-Flörl C. Mucormycosis: from the pathogens to the disease. *Clin Microbiol Infect* 2014;20 Suppl 6:60-66.
72. Spellberg B, Ibrahim A, Roilides E, et al. Combination therapy for mucormycosis: why, what and how? *Clin Infect Dis* 2012;54 Suppl 1:S73-78.
73. Bicanic T, Harrison TS. Cryptococcal meningitis. *Br Med Bull* 2005;72:99-118.
74. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2010;50:291-322.
75. Vail GM, Young RS, Wheat LJ, Filo RS, Cornetta K, Goldman M. Incidence of histoplasmosis following allogeneic bone marrow transplant or solid organ transplant in a hyperendemic area. *Transpl Infect Dis* 2002;4:148-151.
76. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2007;45:807-825.
77. Johnson RH, Einstein HE. Coccidioidal meningitis. *Clin Infect Dis* 2006;42:103-107.
78. Mendoza M, Noel P, Blair JE. Diagnosis, treatment, and outcomes of coccidioidomycosis in allogeneic stem cell transplantation. *Transpl Infect Dis* 2015;17:380-388.
79. Busemann C, Ribback S, Zimmermann K, et al. Toxoplasmosis after allogeneic stem cell transplantation: a single centre experience. *Ann Hematol* 2012;91:1081-1089.
80. Fricker-Hidalgo H, Bulabois CE, Brenier-Pinchart MP, et al. Diagnosis of toxoplasmosis after allogeneic stem cell transplantation: results of DNA detection and serological techniques. *Clin Infect Dis* 2009;48:e9-15.
81. Hernandez AV, Thota P, Pellegrino D, et al. A systematic review and meta-analysis of the relative efficacy and safety of treatment regimens for HIV-associated cerebral toxoplasmosis: is trimethoprim-sulfamethoxazole a real option? *HIV Med* 2016. doi:10.1111/hiv.1240. [Epub ahead of print].
82. Schmidt-Hieber M, Schwender J, Heinz WJ, et al. Viral encephalitis after allogeneic stem cell transplantation: a rare complication with distinct characteristics of different causative agents. *Haematologica* 2011;96:142-149.
83. Ogata M, Fukuda T, Teshima T. Human herpesvirus-6 encephalitis after allogeneic hematopoietic cell transplantation: what we do and do not know. *Bone Marrow Transplant* 2015;50:1030-1036.
84. Hill JA, Koo S, Guzman Suarez BB, et al. Cord-blood hematopoietic stem cell transplant confers an increased risk for human herpesvirus-6-associated acute limbic encephalitis: a cohort analysis. *Biol Blood Marrow Transplant* 2012;18:1638-1648.
85. Inazawa N, Hori T, Yamamoto M, et al. HHV-6 encephalitis may complicate the early phase after allogeneic hematopoietic stem cell transplantation: detection by qualitative multiplex PCR and subsequent quantitative real-time PCR. *J Med Virol* 2016;88:319-323.
86. Reddy SM, Winston DJ, Territo MC, Schiller GJ. CMV central nervous system disease in stem-cell transplant recipients: an increasing complication of drug-resistant CMV infection and protracted immunodeficiency. *Bone Marrow Transplant* 2010;45:979-984.
87. Ljungman P, Perez-Bercoff L, Jonsson J, et al. Risk factors for the development of cytomegalovirus disease after allogeneic stem cell transplantation. *Haematologica* 2006;91:78-83.
88. Hamprecht K, Eckle T, Prix L, et al. Ganciclovir-resistant cytomegalovirus disease after allogeneic stem cell transplantation: pitfalls of phenotypic diagnosis by in vitro selection of an UL97 mutant strain. *J Infect Dis* 2003;187:139-143.
89. Atkinson K, Meyers JD, Storb R, Prentice RL, Thomas ED. Varicella-zoster virus infection after marrow transplantation for aplastic anemia or leukemia. *Transplantation* 1980;29:47-50.
90. Blennow O, Fjaertoft G, Winiarski J, Ljungman P, Mattson J, Remberger M. Varicella-zoster reactivation after allogeneic stem cell transplan-

tation without routine prophylaxis: the incidence remains high. *Biol Blood Marrow Transplant* 2014;20:1646-1649.
91. Steer CB, Szer J, Sasadeusz J, Matthews JP, Beresford JA, Grigg A. Varicella-zoster infection after allogeneic bone marrow transplantation: incidence, risk factors and prevention with low-dose aciclovir and ganciclovir. *Bone Marrow Transplant* 2000;25:657-664.
92. Styczynski J, Reusser P, Einsele H, et al. Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia. *Bone Marrow Transplant* 2009;43:757-770.
93. Tyler KL. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret's. *Herpes* 2004;11 Suppl 2:57A-64A.
94. Aksamit AJ Jr. Progressive multifocal leukoencephalopathy: a review of the pathology and pathogenesis. *Microsc Res Tech* 1995;32:302-311.
95. Durali D, de Goër de Herve MG, Gasnault J, Taoufik Y. B cells and progressive multifocal leukoencephalopathy: search for the missing link. *Front Immunol* 2015;19:241.
96. Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. *Neurology* 2013;80:1430-1438.
97. Reddy P, Davenport R, Ratanatharathorn V, et al. West Nile virus encephalitis causing fatal CNS toxicity after hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2004;33:109-112.
98. Bruno B, Gooley T, Hackman RC, et al. Adenovirus infection in hematopoietic stem cell transplantation: effect of ganciclovir and impact on survival. *Biol Blood Marrow Transplant* 2003;9:341-352.
99. Martino R, Martínez C, Brunet S, Sureda A, López R, Domingo-Albós A. Tuberculosis in bone marrow transplant recipients: report of two cases and review of the literature. *Bone Marrow Transplant* 1996;18:809-812.
100. Girmenia C, Iori AP, Bernasconi S, et al. Listeriosis in recipients of allogeneic bone marrow transplants from unrelated donors. *Eur J Clin Microbiol Infect Dis* 2000;19:711-714.
101. Mansi L, Daguindau E, Saas P, et al. Diagnosis and management of nocardiosis after bone marrow stem cell transplantation in adults: lack of lymphocyte recovery as a major contributing factor. *Pathol Biol (Paris)* 2014;62:156-161.
102. Colosimo M, McCarthy N, Jayasinghe R, Morton J, Taylor K, Durrant S. Diagnosis and management of subdural haematoma complicating bone marrow transplantation. *Bone Marrow Transplant* 2000;25:549-552.
103. Graus F, Saiz A, Sierra J, et al. Neurologic complications of autologous and allogeneic bone marrow transplantation in patients with leukemia: a comparative study. *Neurology* 1996;46:1004-1009.
104. Zhang X, Han W, Chen Y, et al. Intracranial hemorrhage and mortality in 1461 patients after allogeneic hematopoietic stem cell transplantation for 6-year follow-up: study of 44 cases. *Blood* 2013;122:3322.
105. Rabinstein AA, Atkinson JL, Wijdicks EF. Emergency craniotomy in patients worsening due to expanded cerebral hematoma: to what purpose? *Neurology* 2002;58:1367-1372.
106. Bruno B, Gooley T, Sullivan KM, et al. Secondary failure of platelet recovery after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2001;7:154-162.
107. Labrador J, Lopez-Anglada L, Perez-Lopez E, et al. Analysis of incidence, risk factors and clinical outcome of thromboembolic and bleeding events in 431 allogeneic hematopoietic stem cell transplantation recipients. *Haematologica* 2013;98:437-443.
108. Pihusch R, Salat C, Schmidt E, et al. Hemostatic complications in bone marrow transplantation: a retrospective analysis of 447 patients. *Transplantation* 2002;74:1303-1309.
109. Coplin WM, Cochran MS, Levine SR, Crawford SW. Stroke after bone marrow transplantation: frequency, aetiology and outcome. *Brain* 2001;124(Pt 5):1043-1051.
110. Stevens AM, Sullivan KM, Nelson JL. Polymyositis as a manifestation of chronic graft-versus-host disease. *Rheumatology (Oxford)* 2003;42:34-39.
111. Stephenson AL, Mackenzie IR, Levy RD, Road J. Myositis-associated graft-versus-host-disease presenting as respiratory muscle weakness. *Thorax* 2001;56:82-84.
112. Dalakas MC. The role of high-dose immune globulin intravenous in the treatment of dermatomyositis. *Int Immunopharmacol* 2006;6:550-556.
113. Tse S, Saunders EF, Silverman E, Vajsar J, Becker L, Meaney B. Myasthenia gravis and polymyositis as manifestations of chronic graft-versus-host-disease. *Bone Marrow Transplant* 1999;23:397-399.
114. Romi F. Thymoma in myasthenia gravis: from diagnosis to treatment. *Autoimmune Dis* 2011;2011:474512.
115. Lefvert AK, Björkholm M. Antibodies against the acetylcholine receptor in hematologic disorders: implications for the development of myasthenia gravis after bone marrow grafting. *N Engl J Med* 1987;317:170.
116. Bulsara KR, Baron PW, Tuttle-Newhall JE, Clavien PA, Morgenlander J. Guillain-Barré syndrome in organ and bone marrow transplant patients. *Transplantation* 2001;71:1169-1172.
117. Esposito S, Longo MR. Guillain-Barré syndrome. *Autoimmun Rev* 2017;16:96-101.
118. Nasilowska-Adamska B, Lysiak Z, Halaburda K, Szczepinski A, Ejduk A, Maianska B. Guillain-Barré syndrome: pathological connection with GvHD after allogeneic bone marrow transplantation. *Ann Transplant* 2006;11:10-11.
119. Ostronoff F, Perales MA, Stubblefield MD, Hsu KC. Rituximab-responsive Guillain-Barré syndrome following allogeneic hematopoietic SCT. *Bone Marrow Transplant* 2008;42:71-72.
120. Openshaw H, Hinton DR, Slatkin NE, Bierman PJ, Hoffman FM, Snyder D. Exacerbation of inflammatory demyelinating polyneuropathy after bone marrow transplantation. *Bone Marrow Transplant* 1991;7:411-414.
121. Openshaw H. Neurological manifestations of chronic graft versus host disease. In: Vogelsang GB, Pavletic SZ, editors. *Chronic graft-versus-host disease: interdisciplinary management*. New York: Cambridge University Press; 2009:243-251.
122. Grauer O, Wolff D, Bertz H, et al. Neurological manifestations of chronic graft-versus-host disease after allogeneic haematopoietic stem cell transplantation: report from the Consensus Conference on Clinical Practice in Chronic Graft-versus-Host Disease. *Brain* 2010;133:2852-2865.
123. Sostak P, Padovan CS, Eigenbrod S, et al. Cerebral angiitis in four patients with chronic GVHD. *Bone Marrow Transplant* 2010;45:1181-1188.
124. Matsuo Y, Kamezaki K, Takeishi S, et al. Encephalomyelitis mimicking multiple sclerosis associated with chronic graft-versus-host disease after allogeneic bone marrow transplantation. *Intern Med* 2009;48:1453-1456.
125. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124:188-195.
126. Abboud R, Keller J, Slade M, et al. Severe cytokine-release syndrome after T cell-replete peripheral blood haploidentical donor transplantation is associated with poor survival and anti-IL-6 therapy is safe and well tolerated. *Biol Blood Marrow Transplant* 2016;22:1851-1860.
127. Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol* 2015;33:540-549.
128. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. *Lancet* 2015;385:517-528.
129. Jodele S, Laskin BL, Dandoy CE, et al. A new paradigm: diagnosis and management of HSCT-associated thrombotic microangiopathy as multi-system endothelial injury. *Blood Rev* 2015;29:191-204.
130. Laskin BL, Goebel J, Davies SM, Jodele S. Small vessels, big trouble in the kidneys and beyond: hematopoietic stem cell transplantation-associated thrombotic microangiopathy. *Blood* 2011;118:1452-1462.
131. Jodele S, Licht C, Goebel J, et al. Abnormalities in the alternative pathway of complement in children with hematopoietic stem cell transplant-associated thrombotic microangiopathy. *Blood* 2013;122:2003-2007.
132. Uderzo C, Bonanomi S, Busca A, et al. Risk factors and severe outcome in thrombotic microangiopathy after allogeneic hematopoietic stem cell transplantation. *Transplantation* 2006;82:638-644.
133. Kim SS, Patel M, Yum K, Keyzner A. Hematopoietic stem cell transplant-associated thrombotic microangiopathy: review of pharmacologic treatment options. *Transfusion* 2015;55:452-458.
134. de Fontbrune FS, Galambrun C, Sirvent A, et al. Use of Eculizumab in patients with allogeneic stem cell transplant-associated thrombotic microangiopathy: a study from the SFGM-TC. *Transplantation* 2015;99:1953-1959.
135. Au WY, Ma ES, Lee TL, et al. Successful treatment of thrombotic microangiopathy after haematopoietic stem cell transplantation with rituximab. *Br J Haematol* 2007;137:475-478.
136. Zutter MM, Martin PJ, Sale GE, et al. Epstein-Barr virus lymphoproliferation after bone marrow transplantation. *Blood* 1988;72:520-529.
137. Choquet S, Leblond V, Herbrecht R, et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. *Blood* 2006;107:3053-3057.
138. Canova F, Marino D, Trentin C, Solda C, Ghiotto C, Aversa S. Intrathecal chemotherapy in lymphomatous meningitis. *Crit Rev Oncol Hematol* 2011;79:127-134.
139. Heslop HE, Slobod KS, Pule MA, et al. Long-term outcome of EBV-specific T-cell infusions to prevent or treat EBV-related lymphoproliferative disease in transplant recipients. *Blood* 2010;115:925-935.
140. Fukano R, Nishimura M, Ito N, et al. Efficacy of prophylactic cranial irradiation and intrathecal chemotherapy for the prevention of CNS relapse after allogeneic hematopoietic SCT for childhood ALL. *Pediatr Transplant* 2014;18:518-523.