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Review

Neurologic Complications after Allogeneic Hematopoietic Stem Cell Transplantation

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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.

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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

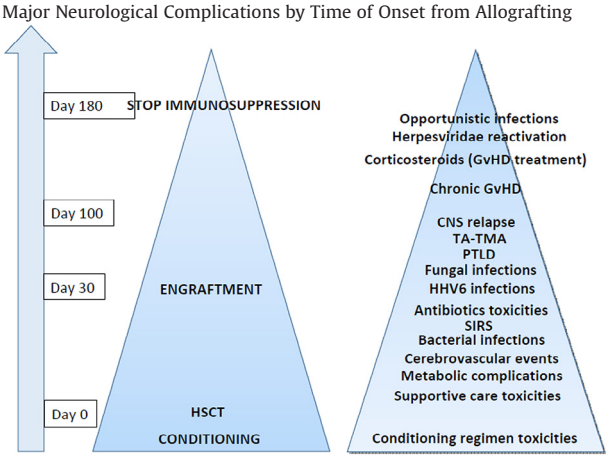
CNS indicates central nervous system; cGVHD, chronic graft versus-host disease; CRS: cytokine release syndrome.

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