Acute symptomatic seizures during haematopoietic stem cell transplantation in patients with leukemia: State of art

Alexey Yu. Polushin, Iaroslav B. Skiba, Mikhail O. Sadovskih, Maria D. Vladovskaya, Alexander D. Kulagin

Pavlov University, St. Petersburg, Russia

SUMMARY

Acute symptomatic epileptic seizures are among common complications of hematopoietic stem cell transplantation. The etiological factors leading to the development of this condition differ from those in general population, while the significance of each of them is different and depend on the time point post-transplant. In this article, we analyze the literature data on the role of drug effects, metabolic disorders and infectious complications, as well as pathologies of brain substance in development of acute symptomatic seizures in patients with oncohematological diseases. We also considered the clinical features of symptomatic epileptic seizures and potential prognostic significance of their development in patients who has undergone hematopoietic stem cell transplantation.

Keywords: leukemia, epileptic seizures, generalized tonic-clonic seizures, cytokine release syndrome, transplantation, hyponatremia, hematopoietic stem cells, busulfan.

INTRODUCTION

Currently, hematopoietic stem cell transplantation (HSCT) is an effective treatment option for malignant (acute leukemia, myelodysplastic syndrome) and nonmalignant (e.g., aplastic anemia) diseases of the blood system, as well as a number of autoimmune diseases, solid tumors and hereditary diseases in children and adolescents [1, 2]. With introduction of new highly effective polychemotherapy regimens into clinical practice, the use of HSCT has significantly increased the survival rate of patients with almost all clinical forms of leukemia [3-5]. Neurological complications during HSCT can affect the survival rate of patients and alter the full implementation of the therapy protocol [6]. A similar statement can be formulated not only for neurological complications of HSCT in general, but also for acute symptomatic epileptic seizures (ASES) [7]. At present, the spectrum of neurological complications and the frequency of their occurrence was significantly changed due to a trend to decreasing intensity of conditioning regimens and expanding range of immunotherapy in patients with onco-hematological diseases [8]. This fact determines the need for analyzing the currently available data regarding the incidence, etiology, clinical performance and prognostic significance of ASES in oncohematologic patients. The purpose of our study was to collect, analyze and discuss the research publications on etiology, semiotics and prognostic significance of ASES in patients undergoing hematopoietic stem cell transplantation.

MATERIALS AND METHODS

In accordance with the main goal, a search was made for scientific publications in the databases "Pubmed", "Scopus". The search algorithm included search queries for "allogeneic HSCT", "stem cell", "acute symptomatic epileptic seizures" and "epileptic seizures".

ETIOLOGICAL FACTORS IN THE DEVELOPMENT OF ASES

In patients after HSCT, the incidence of ASES reaches 6.9-11.7%, depending on the cohorts of patients. ASES are observed significantly more often (52.6-75.0%) in presence of other neurological complications [9]. In oncohematologic patients, ASES may have distinct clinical features and variable prognostic significance, and they can occur both before HSCT and in the post-transplant period. The profile of etiologic factors leading to the development of ASES in this cohort of patients differs from that in the general population. Basically, this pattern has one main feature: the list of risk factors for seizures does not include febrile convulsions,

How to cite this article: Polushin AYu, Skiba IB, Sadovskih MO, et al. Acute symptomatic seizures during haematopoietic stem cell transplantation in patients with leukemia: State of art. Cell Ther Transplant. 2025; 14(3): 31-42

doi: 10.18620/ctt-1866-8836-2025-14-3-31-42
EDN: DRRQZF
Submitted: 10 April 2025, accepted: 30 September 2025

Correspondence: Dr. Alexey Yu. Polushin, Pavlov, 6-8 L.Tolstoy St, 197022, St. Petersburg, Russia

Phone: +7 (911) 816-75-59
E-mail: alexpolushin@yandex.ru

which are the cause of ASES in more than 1/3 of all cases in the general population [10]. In a cohort of oncohematologic patients, the etiologic factors for the development of ASES are as follows (Fig. 1):

- Drug therapy (immunosuppressants, antimicrobials, dimethyl sulfoxide);
- Metabolic disorders;
- Structural damage of brain substance, e.g., ischemic stroke, intracranial haemorrhage, posterior reversible encephalopathy syndrome (PRES);
- Infectious complications (meningitis, encephalitis, systemic infection);
- Specific damage to the central nervous system (CNS) in leukemia and other tumor diseases, including in the variant of extramedullary recurrence after HSCT.

Total or partial irradiation therapy as a part of conditioning regimens may be also added to this list. The mentioned etiologic factors in development of ASES are also dominant at the pre-transplant period, differing in their significance for the patients who received polychemotherapy, and those who were not subject to such treatment. One may also argue that the relative significance of above mentioned factors depends on the terms after HSCT.

MEDICINAL DRUGS OF CONCERN

General overview of HSCT-associated therapies

Drug-induced epileptic seizures account for under 6% of all cases of ASES in the general population [11]. Among the causes of *status epilepticus*, drug toxicity is also far from the first place, being the cause of its development in less than 5% of cases [12]. Meanwhile, the role of this factor for seizure provocation is significantly higher (8-41.8%) among the HSCT patients [7, 9], especially in children (39%) [13]. In patients undergoing HSCT, a number of drugs may provoke ASES (Table 1).

It is difficult to evaluate the incidence of ASES depending on the specific drug because of the different definitions of the term ASES itself. Medical guidelines often use non-specific terms such as "seizures" and "convulsive seizures", which may differ from the International League Against Epilepsy's definition of ASES [47] and the definition in Common Terminology Criteria for Adverse Events (CTCAE) 5.0 [48].

Cytostatic and immunosuppressive drugs

Busulfan can be considered as one of the main drugs that can provoke the development of ASES. The results of retrospective registry studies show that the frequency of ASES in busulfan administration is 1.3-6.7% if provided prophylactic therapy with antiepileptic drugs (AEDs) for the period of this drug administration [14; 15]. Along with busulfan, a range of other cytostatic drugs, including those injected intrathecally, may lead to the development of ASES (e.g., methotrexate).

According to various reports, the incidence of ASES during therapy with calcineurin inhibitors (tacrolimus, cyclosporine A) is 5-11% [49, 50]. A number of studies have shown that a possible mechanism for the development of epileptic seizures during cyclosporine therapy is the ability of this drug to

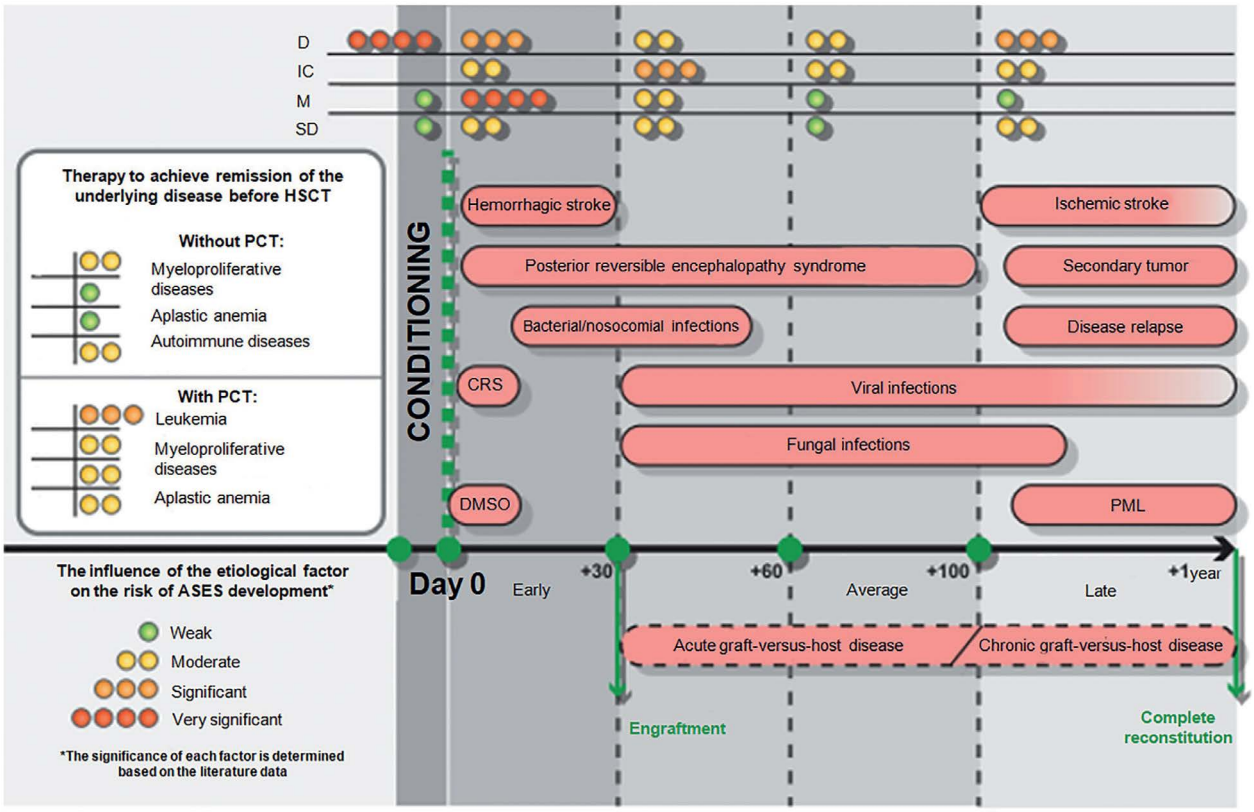

Figure 1: Etiological factors of acute symptomatic epileptic seizures during HSCT

Abbreviations: CR, cytokine release syndrome; D, drugs; IC, infectious complications; MD, metabolic disorders; SD, structural damage (of brain substance); PCT, polychemotherapy; PML, progressive multifocal leukoencephalopathy

Table 1: Medical drugs used in the course of HSCT that can potentially provoke ASES

Group of drugs	Drug	Rate of ASES*, according to instruction**	Published ASES rate	Reference
Preparations of the conditioning mode				
Chemotherapy drugs	Bendamustine	Side effect not specified	No data	-
	Busulfan	Rare (when using high doses)	1.3-6.7%	[14, 15]
	Carmustine	Side effect not specified	9-38% (specific clinical situations)***	[16]
	Melphalan	Side effect not specified	3.1% (in combination with bortezomib therapy)	[17]
	Platinum drugs	Side effect not specified	Specific clinical cases	[18]
	Thiophosphamide	Side effect not specified	Specific clinical cases (co-administration with carboplatin)	[19]
	Fludarabine	Rare	0.5%	[20]
	Cyclophosphamide	Side effect not specified	Specific clinical cases	[21, 22]
	Cytarabine (high doses)	Rare	Specific clinical cases	[23]
	Etoposide	Side effect not specified	Specific clinical cases	[18]
Drugs accompanying the hematopoietic stem cells infusion				
Cryoprotector	Dimethylsulfoxide	Side effect not specified	Specific clinical cases	[24-26]
Drugs for the prevention and treatment of the graft-versus-host disease				
Immunosuppressants	Methotrexate	Rare	0.2%; specific clinical cases	[27, 28]
	Mycophenolatmofetil	Side effect not specified	Specific clinical cases (including when combined with cyclosporine)	[29, 30]
	Ruxolitinib	Side effect not specified	No data	–
	Sirolimus	Side effect not specified	No data (prospective randomized trials are being conducted to evaluate the epileptic effect of the drug)	[31]
	Tacrolimus	Frequent	9.1-14.8%	[32, 33]
	Cyclosporine A	Rare	A large number of clinical cases	[34]
	Everolimus	Side effect not specified	No data (prospective randomized trials are being conducted to evaluate the epileptic effect of the drug)	[35]
	Etanercept	Rare	Specific clinical cases	[36]
Drugs for the prevention and treatment of infectious complications				
Antibacterial drugs****	Amikacin	Rare	No data	–
	Vancomycin	Side effect not specified	No data	–
	Imipenem	Rare	0.4%	[37]
	Colistin	Side effect not specified	No data	–
	Co-trimaxosol	Side effect not specified	Specific clinical cases	[38]
	Linezolid	Not frequent	Specific clinical cases	[39]
	Meropenem	Specific clinical cases	0.7%	[37]
	Penicillins	Rare, or not indicated as a side effect	Series of clinical cases	[40]
	Tigecycline	Side effect not specified	No data	–
	Cephalosporins	Rare	Series of clinical cases	[41, 42]
	Ciprofloxacin	Rare	Specific clinical cases	[43]
Antiviraldrugs****	Acyclovir	Very rare	No data	–
	Valganciclovir	Very rare	No data	–
	Ganciclovir	Very rare	Specific clinical cases	[44]
	Cidofovir	Side effect not specified	No data	–
Antifungal drugs****	Amphotericin B	Rare	No data	–
	Anidulafungin	Side effect not specified	No data	–
	Voriconazole	Rare	No data	–
	Intraconazole	Side effect not specified	Specific clinical cases (in combination with vincristine)	[45]
	Caspofungin	Side effect not specified	No data	–
	Posaconazole	Rare	Specific clinical cases (in combination with vincristine)	[46]

Note: *The definitions from the drug instructions were taken into account: "epileptic seizure", "convulsive seizure", "convulsions". ** Frequency of side effect: very often (>1/10), often (from >1/100 to <1/10), infrequently (from> 1/1000 to <1/100), rarely (from >1/10000 to <1/1000), very rare (<1/10000). *** In the early postoperative period after surgical treatment of gliomas followed by implantation of carmustine reservoir. **** Indicates drugs and groups of drugs used for the prevention and treatment of infectious complications according to the in-hospital protocol at the Gorbacheva Research Institute for Pediatric Oncology, Hematology and Transplantation (St. Petersburg).

reduce the concentration of gamma-aminobutyric acid (GABA) in neurons, decrease the activity of GABAergic neurons, and reduce the ability of GABA receptors to bind gamma-aminobutyric acid molecules [51, 52]. Such pharmacologic mechanisms may contribute to the development of ASES [53]. Also decreased N-acetylaspartate (NAA) concentration [51], as well as electrolyte disturbances and microglia damage [54] may be considered the possible proconvulsive mechanisms of cyclosporine. Epileptic seizures have also been described as a side effect of tacrolimus, another drug from the group of calcineurin inhibitors. At the same time, the possible mechanism of ASES development during the therapy with this drug is different from that of cyclosporine. Given the presence of cyclophilin, calmodulin, and tacrolimus-binding protein in brain tissue, it is the direct effect of tacrolimus *via* calcineurin that can trigger a cascade of irreversible changes in brain matter with the generation of an epileptogenic substrate [32, 55].

Dimethylsulfoxide (DMSO), being an essential component of stem cell cryopreservation, may also be a cause of ASES [24, 25]. Unfortunately, there are no cohort studies on the association of DMSO with epileptic seizures, and only isolated observations are presented in the literature. For instance, in the publication of O. Hequet et. al. (2002), the development of a series of generalized tonic-clonic seizures was observed 10 minutes after starting the stem cell infusion; when EEG was performed 3 hours after seizure control, diffuse discharges of "acute-slow wave" complexes were detected [26]. Formation of sulfite compounds is suggested among possible mechanisms for development of epileptic seizures during DMSO administration which exert a dramatically negative effect on mitochondrial functions [56]. Even though this agent is quite safe in use, other neurological complications associated with usage of this compound have been described in the literature. For example, ischemic stroke and myocardial infarction that have been described elsewhere could develop due to prolonged and acutely developing vascular constriction [57]. In summary, the small number of reports on neurotoxic manifestations on the background of DMSO administration is associated with dose-dependent reactions to the drug administration (currently, DMSO is used at lower concentrations than previously) [58].

One may assume that the development of ASES associated with the use of DMSO can be expected during injection, or within first hours after its administration. One may consider the possibility of concomitant ischemic damage to the brain substance due to vasoconstriction as an independent cause of subsequent ASES occurence.

Antimicrobial drugs

A range of antibiotics are neurotoxic and may cause epileptic seizures. Antibacterial, antiviral, and antifungal therapy is prescribed to all HSCT patients, either for primary antimicrobial prophylaxis or to treat complications of transplantation (e.g., febrile neutropenia) [59]. Therefore, the possibility of epileptic seizures may be considered as a complication of such therapy when determining the possible causes of paroxysmal conditions. Linezolid-induced epileptic seizures [39] and *status epilepticus* upon usage of this drug [60] have been described in the literature. The *status epilepticus* has been also been described during intravenous use of cephalosporins, and the risk of developing this side effect is particularly high in patients with impaired renal function [61]. Various types of epileptic seizures (including myoclonias) have been described with penicillin [62]. For some drugs there is no evidence of direct neurotoxic effect, however, their use may be accompanied by the development of epileptic seizures due to metabolic disorders, for example, marked hypoglycemia during therapy with co-trimaxol [38].

A meta-analysis published by Cannon et al. demonstrated that carbapenem use was associated with an 87% increased risk of epileptic seizures (OR 1.87; 95% CI 1.35-2.59; p=0.031; I^2=30.8%) compared to the use of antibiotics of other classes (absolute value 2 cases *per* 1000 patients) [37]. The highest risk of epileptic seizures was observed with imipenem treatment (OR 3.50; 95% CI 2.23 to 5.49; p=0.01); however, these data must be interpreted through a direct comparison of imipenem with other carbapenems. Indeed, imipenem was associated with a statistically insignificant increased risk of epileptic seizures compared with meropenem (OR 1.48; 95% CI 0.54-4.04; p=0.92; I^2=0.0%).

Antifungals have also been associated with the development of acute and symptomatic epileptic seizures in a series of clinical cases [46]. The necessity to consider antibiotics as a risk factor for the development of epileptic seizures is confirmed by the results of a neurosurgical study [63] in which intraoperative use of antibiotics (cefazolin irrigation) during craniotomy was strictly associated with development of epileptic seizures.

Therefore, a wide range of drugs from different groups used in patients both at the pre-transplantation stage and at different time periods in the post-transplant period can lead to the development of ASES. It should be noted that an extra risk factor for ASES development may be related to drug interactions, both between chemotherapeutic drugs and between them and concomitant therapy drugs. The increased risk of ASES development in these situations may be due to both the increased concentration of the drugs themselves and the increased number of cases of complications from the therapy. For instance, inclusion of phenytoin in the treatment regimen may lead to a higher incidence of renal failure requiring dialysis (OR 0, 44; 95% CI 0.28-0.71; p<0.001) compared with the use of other anticonvulsants (e.g., levetiracetam) [64].

Metabolic disorders in HSCT patients

Metabolic disorders and electrolyte disturbances present a well-known problem in oncohematologic patients but are not in the focus of systematic analysis [65]. Electrolyte disturbances are the cause of 8% of all ASES in the general population [13], and in the group of patients who underwent HSCT, with increased significance of this factor for epileptic attacks, reaching 13.9% [7]. The role of electrolyte disturbances in the development of epileptic seizures and epileptogenesis is sufficiently studied and consists in disruption of synaptic (inhibitory/excitatory) interaction between neurons [66]. Oncohematological patients are characterized by a wide variety of electrolyte disturbances, which can be caused by the cancer process itself, infiltration of organs by malignant cells, tumor cell death, side effects of treatment [67], as well as observed in the structure of "genesis syndrome" (increased consumption

of potassium and phosphorus by the transplanted donor cells during active recovery of hematopoiesis) [68]. At the same time, specific types of electrolyte imbalances (in particular, hyponatremia) can be caused by relatively rare conditions, such as the development of the renal salt-wasting syndrome [69]. Patients undergoing HSCT may have an increased risk of electrolyte abnormalities compared to oncohematology patients who have not undergone the procedure. In a study by Philibert et al. [70] among patients who received autologous HSCT, 81% showed low potassium levels, and 67% developed hypomagnesemia. Meanwhile, the electrolyte disturbances in this group appeared on D+11 after HSCT.

The most common electrolyte disturbances associated with epileptic seizures are listed below (Table 2). Anticonvulsants can also cause electrolyte imbalances, such as hyponatremia. The epileptic seizure may transiently increase blood sodium levels, making it difficult to diagnose electrolyte disturbances. Therefore, it is important to monitor electrolyte levels in patients undergoing HSCT, as the development of these disorders can have a diverse genesis and may occur at different times after HSCT. Confirmation or exclusion of an electrolyte imbalance should be a standard part of care for patients with ASES.

Structural brain damage

During HSCT, several complications may occur that can cause structural brain damage. These complications include acute ischemic and hemorrhagic strokes, development of secondary CNS tumors, autoimmune demyelination in CNS, as well as specific syndromes (e.g., PRES). PRES is of particular concern due to its higher incidence among oncology patients compared to the general population and its specific risk factors. PRES is the cause of ASES after HSCT in 1.1-22% of cases, more often observed in children [74]. Compared to the clinical pattern of PRES in the general population (ASES in 66% of patients) [75], ASES manifests in 97% of PRES cases in oncohematology patients, being more often observed in the early post-HSCT period (64% of all ASES patients) [74]. Cytotoxic therapy can be considered one of the major risk factors for PRES development [76]. Therefore, in a study by Gaziev et al. (2017), all cases of PRES (n=31; 11% of total sample) were interpreted as a side effect of calcineurin inhibitor therapy (tacrolimus and cyclosporine) [77]. Several complications of HSCT may act as risk factors for PRES, as shown in a study by Q. Chen et al. (2020), in a mixed group of patients (adults and children); acute GvHD of II-IV degree was the risk factor for PRES (OR 2.370, 95% CI 1.277-4.397; p=0.006) [74]. The results of evaluating etiological factors for development of this syndrome in the general population emphasize the special profile of risk factors for PRES in patients with HSCT. A retrospective analysis of 127 PRES cases showed that arterial hypertension was the main cause of its development (72%) [75].

Total body irradiation

The use of total body irradiation (TBI) as a part of conditioning regimen before HSCT can lead to the development of complications, including stroke-like migraine attacks after radiation therapy syndrome, known as SMART syndrome. Although the SMART syndrome is usually associated with brain irradiation at doses of 50 Gy or higher [78], its occurrence has also been reported at lower doses [79; 80]. Therefore, it is possible that patients undergoing HSCT with TBI may develop SMART and related epileptic seizures.

Immune damage to the nervous system is considered a potential factor in the development of autoimmune and inflammatory diseases. The key concepts related to this issue are cytokine release syndrome and cytokine storm. These terms refer to the release of a large number of cytokines by activated immune cells, leading to systemic inflammation and multiorgan damage [81].

Activation of immune cells can occur due to infectious agents [82] or drug therapy [83]. The leading mediators of systemic inflammation may vary, including tumor necrosis factor-alpha, interleukin-6, and interferon-gamma. As a result of these pathological conditions, immune effector cell-associated neurotoxicity syndrome (ICANS) can develop. This condition is associated with damage to the blood-brain barrier (BBB) and endothelial dysfunction, leading to encephalitis, ischemic brain damage [84], or intracerebral hemorrhage [85]. In addition, increased permeability of the BBB may lead to development of neurotoxicity during therapy [86]. As a result, the occurence of cytokine release syndrome and cytokine storm in patients may cause structural damage of brain substance, which is a risk factor for the development of ASES.

Based on the analysis of the etiological factors that contribute to the development of ASES in patients undergoing HSCT, one may conclude on significant diversity in these factors and that certain factors may have a greater impact in this population compared to the general population. Moreover, it is possible that several etiological factors for epileptic seizures occur concurrently, leading to a higher incidence of ASES when CNS complications are present.

Table 2: Threshold levels of electrolyte disturbances most commonly resulting in acute epileptic seizures (mmol/L)

Type of electrolyte disturbances	Mild	Moderate	Pronounced
Hyponatremia	130-134	125-129	<125
Hypernatremia	145-149	150-169	≥170
Hypocalcemia	1.9-2.2		≤1.9
Hypercalcemia	2.5-3	3.0-3.5	3.5-4.0
Hypomagnesemia	0.8-1.6		<0.8

Clinical features of acute symptomatic seizures in HSCT patients

Generalized tonic-clonic seizures (GTCS) have been considered the most common type of epileptic seizures in patients with HSCT [6]. In a study by Zhang et al. [7], 60.8% of patients had a combination of focal motor seizures, focal seizures without motor manifestations, and GTCS. The analysis of semiotics of epileptic seizures in the pediatric population with HSCT revealed that eye deviation is one of the most common symptoms in seizures with and without loss of consciousness [9]. It is important to note that high doses of busulfan can lead to myoclonias [87], which may not be epileptic [88].

One of the important aspects to consider is the time after HSCT when ASES is most likely to occur. In a study by Zhang et al. (2013), the most frequent epileptic seizures (65.8%) occurred in the early posttransplant period. These data are consistent with other studies showing that CNS complications after HSCT generally occur in the early post-transplant period, both in adults [89] and children [6]. The study by Kang et al. [6] has also shown that the use of calcineurin inhibitors is associated with earlier development of neurological complications, including epileptic seizures. The increased frequency of ASES in the early post-transplant period is supported by the findings of Khan et al. [13] who have shown that ASES occurred relatively early in oncohematology patients who were not referred for HSCT. The median time from diagnosis to ASES was 6 months during periods of remission and consolidation [13]. This finding suggests that therapy for oncohematological diseases is a major risk factor for ASES development. This confirms the importance of drugs in triggering epileptic seizures in this patient group.

Epileptic seizure cannot be considered as an independent factor influencing the survival rate of patients after HSCT, due to a wide range of its causes included in the structure of HSCT-associated mortality, or with recurrence of the underlying disease. Similar analysis was carried out only in single retrospective studies. Thus, in the study of Zhang et al., the survival rate of patients within first 100 days after HSCT was 83.8% in the group of patients with epileptic seizures and 93.2% in the group of patients without epileptic seizures ($p=0.072$). The statistically significant differences between these groups were obtained when assessing survival at 1 year (57.2% vs 75.7%; $p=0.015$) and 6 years after HSCT (31.1 vs 71.4%; $p<0.001$) [7]. The same study has demonstrated that the survival rate depends on the cause of neurologic complications in the group of patients with epileptic seizures. Thus, patients who developed epileptic seizures due to drug neurotoxicity, or metabolic disorders had a higher 6-year survival rate (45.8% and 51.9%, respectively), compared to patients with epileptic seizures caused by infectious complications (10.8%).

DISCUSSION

The present literature review provides a comprehensive overview of the etiologic factors, clinical features, and prognostic significance of ASES in oncohematological patients undergoing HSCT. However, there are several issues that require further discussion. E.g., a special problem concerns validity of prophylactic AEDs prescription when busulfan is administered, since busulfan is an alkylating cytostatic drug that easily penetrates the blood-brain barrier and may cause seizures. According to the medical guidelines, seizures may occur during treatment with high doses of busulfan, and the patients should receive preventive anticonvulsant therapy. Benzodiazepines should be used preferably, rather than phenytoin. The data on 1.3-6.7% frequency of ASES events in busulfan treatment may be compared with results of individual case reports, where this complication was not observed in any patient. One should also consider that most of these studies included patients treated with monotherapy using different AEDs (carbamazepine, levetiracetam, valproic acid, diphenyl, benzodiazepines) during the entire course of busulfan administration.

According to the literature, the neurotoxic effect of busulfan is thought to be due to its ability to cross the blood-brain barrier. These data are supported by appropriate guidelines for usage of the drug, thus providing some legal justification for usage of AEDs in busulfan therapy. However, this information alone does not provide any scientific evidence for real efficacy of this approach.

In 2012, the *American J Haematology* published a letter to the editor with the eloquent title "Outdated Dogma? Busulfan, Epileptic Seizures and HSCT" [91]. The authors concluded, "we believe that routine use of anticonvulsant prophylaxis in patients receiving busulfan chemotherapy, regardless of the dose, or route of administration, is another example of an outdated clinical practice that persists despite a paucity of good-quality supporting medical evidence". Indeed, the prescription of anticonvulsants during busulfan therapy (primary prophylaxis of ASES) is very common and is mentioned in the protocols of allo-HSCT, taking into account local clinical guidelines. But did the authors rightly point out lacking evidence for advantage of such approach? May be, the opposite strategy (non-use of AEDs in busulfan therapy) could be also proven?

Analysis of the literature on this topic reveals lacking data on phase II and phase III studies on busulfan clinical trials with free access, as well as any prospective or retrospective comparisons between AED prescription versus non-prescription strategies during busulfan treatment. Most publications concern effectiveness of individual anticonvulsant drugs [14, 90, 92, 93], as well as on comparing their relative efficiency. A common item in these studies is not only the comparison of efficacy, but also the safety of this therapy. The treatment safety is determined by the potential for drug interactions between busulfan and AEDs [94]. For instance, Carreras et al. (2010) showed that busulfan clearance was increased by more than 10% when combined with clonazepam compared to phenytoin [95]. These figures become even more important, given that phenytoin, as an independent drug, increases the busulfan clearance by 15%. No wonder that the emergence of new-generation AEDs with safer pharmacokinetic profile has changed the range of AEDs used to prevent busulfan-induced ASES.

In a study by Tsujimoto et al. (2020), when comparing the efficacy of levetiracetam and clonazepam in children undergoing busulfan treatment, levetiracetam showed a more favorable tolerance profile. Specifically, dizziness and irritability,

observed in the clonazepam group (54% and 62%, respectively), were not reported in the levetiracetam group [15]. This study may be an example of shifting approach to prevention of epileptic seizures during busulfan therapy. It should be noted, however, that the authors also mention the occurrence of other adverse events, such as ASES, without the use of AEDs. The authors refer to the review by Eberly et al. (2008), with data based on the analysis of available literature [98]. The frequency of epileptic seizures in presence of busulfan therapy 40% was obtained in a group of 5 patients [99]. The same review referred to the studies with a larger sample size (n=57), with a significantly lower incidence of seizures (1.8%) [100]. The latter study was the largest to evaluate the results of AEDs application during busulfan treatment, but it was conducted more than 30 years ago.

Thus, the only conclusion that may be drawn is that the use of newer generation AEDs, such as levetiracetam, is preferable to that of the earlier used drugs, such as phenytoin. However, due to lack of sufficient scientific evidence, it is not possible to make a definitive statement about efficiency of AED prescription during busulfan treatment.

In addition, it is important to consider the context of using preventive therapy with AEDs. When an epileptic seizure occurs, busulfan treatment is usually canceled, or the drug dose is reduced, thus leading to reduced intensity in conditioning before HSCT. This, in turn, may affect the outcome of treatment. Therefore, administration of AEDs appears to modify a risk factor by reducing the frequency of seizures and potentially decreasing the risk of complications from treatment for the underlying disease.

In our opinion, the problem of AED usage in busulfan therapy can only be resolved by conducting a prospective study comparing two treatment strategies: the prescription of AEDs or refusal of such therapy. At present, it is difficult to conduct such a study due to the following reasons:

- ethical issues (difficulty in conducting a placebo-controlled trial in oncohematologic patients).
- legal issues (presence of official instructions in the medical guidelinesfor the drug busulfan for the use of AEDs).
- practical issue (wide adherence of hematologists to routine administration of AEDs).
- institutional issues. In a study comparing two approaches (with and without AED prescriptions), given a known frequency of epileptic seizures (0.5% on AED therapy *versus* 1.8% without AED therapy), with a margin of error of 0.05 and study power of 0.8, a group size of, at least, 1,000 patients would be required to detect statistically significant differences between the two approaches.

Another issue that needs to be addressed is the role of electrolyte disturbances as a risk factor for acute and chronic GvHD in patients after allogeneic HSCT. With allo-HSCT, electrolyte abnormalities are often seen in both acute and chronic GvHD. In acute GvHD, these disturbances may be due to damage to the gastrointestinal tract, manifesting as profuse diarrhea, recurrent vomiting, and impaired gut absorption, as well as an alimentary factor (the patients require a low-salt diet) [101].

When considering statistical methods for determining risk factors for ASES development, it should be noted that the published results are based on single-factor analysis. Multivariate analysis has been used in very few studies, e.g., a work by Zhang et al. (2013). It was found that, in subjects <18 years old, the type of HSCT donor, presence of acute GvHD, and hyponatremia (<135 nmol/L) were significant risk factors for ASES in a cohort of patients undergoing allo-HSCT [7]. Absence of a statistically significant contribution from a group of drugs or specific drugs to the multifactorial model may be due to coinciding or overlapping effects of different factors on ASES risk. This phenomenon may explain why ASES is not included in multifactorial models predicting patient survival after HSCT.

CONCLUSION

ASES is a significant neurological complication in HSCT patients, which develops usually in the early post-transplant period. The profile of factors causing ASES in HSCT differs from that in the general population. The same risk factor (e.g., drug use) may be both a direct cause of ASES and may lead to conditions (e.g., PRES) that may cause this complication. The use of some medications may increase the risk of ASES earlier after HSCT. Assessment of ASES origins in distinct cases determines the differential prognostic value of this complication, depending on the specific causal and pathogenetic factors.

CONFLICT OF INTEREST

The study had no sponsorship. Authors declare no conflict of interest. The authors are fully responsible for submitting the final version of the manuscript. All the authors took part in the development of the concept of the article and the writing of the manuscript. The final version of the manuscript was approved by all authors.

COMPLIANCE WITH ETHICAL PRINCIPLES

The authors confirm that they respect the rights of the people participated in the study, including obtaining informed consent when it is necessary, and the rules of treatment of animals when they are used in the study. Author Guidelines contains the detailed information.

REFERENCES

1. Afanas'ev BV, Zubarovskaya LS, Moiseev IS. Allogeneic transplantation of hematopoietic stem cells in children: present state, issues and prospectives. Russian Journl of Pediatric Hematology and Oncology. 2017;2 (2):28–42. (In Russian). doi: 10.17650/2311-1267-2015-2-2-28-42
2. Afanas'ev BV, Afanas'eva KB, Barabanshchikova MV, et al. Indications for hematopoietic stem cell transplantation. Cell Ther Transplant. 2019; 8(4):101-145. doi: 10.18620/ctt-1866-8836-2019-8-4-101-145
3. Parovichnikova EN, Savchenko VG. Russian multicenter clinical trials in acute leukemias. Terapevticheskyi Arkhiv. 2019; 91(7): 4-13. (In Russian). doi: 10.26442/00403660.2019.07.000325
4. Bondarenko SN, Moiseev IS, Slesarchuk OA, Darskaya EI, Ekushev KI, Smirnova AG, et al. Allogeneic hematopoietic stem cell transplantation in children and adults with acute lymphoblastic leukemia. Cell Ther Transplant. 2016; 5(2):12-20. doi: 10.18620/1866-8836-2016-5-2-12-20

5. Paina OV, Rakhmanova ZhZ, Kozhokar PV, Frolova AS, Tsvetkova LA, Razumova SV, et al. Results of allogeneic haematopoietic stem cell transplants from compatible unrelated or related haploidentical donors in children with high-risk infant leukemias in 1st and 2nd remissions. Voprosy gematologii/onkologii i immunopatologii v pediatrii. 2020;19(2):30-37. (In Russian). doi: 10.24287/1726-1708-2020-19-2-30-37
6. Kang JM, Kim YJ, Kim JY, et al. Neurologic complications after allogeneic hematopoietic stem cell transplantation in children: analysis of prognostic factors. Biol Blood Marrow Transplant. 2015; 21(6):1091-1098. doi: 10.1016/j.bbmt.2015.02.007
7. Zhang XH, Xu LP, Liu DH, et al. Epileptic seizures in patients following allogeneic hematopoietic stem cell transplantation: a retrospective analysis of incidence, risk factors, and survival rates. ClinTransplant. 2013;27(1):80-89. doi: 10.1111/ctr.12000
8. Wieczorek M, Mariotto S, Ferrari S, Mosna F, Micò MC, et al. Neurological complications in adult allogeneic hematopoietic stem cell transplant patients: Incidence, characteristics and long-term follow-up in a multicenter series. Bone Marrow Transplant. 2022; 57(7):1133-1141. doi: 10.1038/s41409-022-01690-x
9. Cordelli DM, Masetti R, Zama D, et al. Etiology, characteristics and outcome of seizures after pediatric hematopoietic stem cell transplantation. Seizure. 2014;23(2):140-145. doi: 10.1016/j.seizure.2013.11.003
10. Lipatova LV, Rudakova IG, Sivakova NA, Kapustina TV. Acute symptomatic epileptic seizures and status epilepticus. Zh Nevrol Psikhiatr Im SS Korsakova. 2015; 115(4): 24-29. (In Russian) doi: 10.17116/jnevro20151154124-29
11. Annegers JF, Hauser WA, Lee JR Rocca WA. Incidence of acute symptomatic seizures in Rochester, Minnesota, 1935-1984. Epilepsia. 1995; 36(4):327-333. doi: 10.1111/j.1528-1157.1995.tb01005.x. PMID: 7607110
12. Costello DJ, Cole AJ. Treatment of acute seizures and status epilepticus. J Intensive Care Med. 2007; 22(6):319-347. doi: 10.1177/0885066607307506
13. Khan RB, Morris EB, Pui CH, et al. Long-term outcome and risk factors for uncontrolled seizures after a first seizure in children with hematological malignancies. J Child Neurol. 2014; 29(6): 774-781. doi: 10.1177/0883073813488675
14. Caselli D, Ziino O, Bartoli A, Santangelo G, Vanadia F, Aricò M. Continuous intravenous infusion of lorazepam as seizure prophylaxis in children treated with high-dose busulfan. Bone Marrow Transplant. 2008; 42(2):135-136. doi: 10.1038/bmt.2008.91. PMID: 18372906
15. Tsujimoto SI, Shirai R, Utano T, et al. Comparison of clonazepam and levetiracetam in children for prevention of busulfan-induced seizure in hematopoietic stem cell transplantation. Int J Hematol. 2020; 111(3):463-466. doi: 10.1007/s12185-019-02795-8
16. Della Puppa A, Denaro L, Rossetto M, Ciccarino P, Manara R, Lombardi G., et al. Postoperative seizure in high grade glioma patients treated with BCNU wafers. A mono-institutional experience. J Neurooncol. 2011; 105(2):275-280. doi: 10.1007/s11060-011-0577-6. PMID: 21505945
17. Biran N, Rowley SD, Vesole DH, et al. A Phase I/II Study of escalating doses of bortezomib in conjunction with high-dose melphalan as a conditioning regimen for salvage autologous peripheral blood stem cell transplantation in patients with multiple myeloma. Biol Blood Marrow Transplant. 2016; 22(12):2165-2171. doi: 10.1016/j.bbmt.2016.08.017. PMID: 27590107
18. Ryan SA, Maceneaney P, O'Reilly SP, Moylan EJ, Power DG. Reversible posterior leukoencephalopathy induced by carboplatin and etoposide. Med Oncol. 2012; 29(2):1287-1291. doi: 10.1007/s12032-011-9898-8. PMID: 21390516
19. Kushner BH, Cheung NK, Kramer K, Dunkel IJ, Calleja E, Boulad F. Topotecan combined with myeloablative doses of thiotepa and carboplatin for neuroblastoma, brain tumors, and other poor-risk solid tumors in children and young adults. Bone Marrow Transplant. 2001; 28(6):551-556. doi: 10.1038/sj.bmt.1703213
20. Beitinjaneh A, McKinney AM, Cao Q, Weisdorf DJ. Toxic leukoencephalopathy following fludarabine-associated hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2011; 17(3):300-308. doi: 10.1016/j.bbmt.2010.04.003. PMID: 20399878
21. Meldgaard Knudsen L, Jensen L, Gaarsdal E, Nikolaisen K, Johnsen HE. A comparative study of sequential priming and mobilisation of progenitor cells with rhG-CSF alone and high-dose cyclophosphamide plus rhG-CSF. Bone Marrow Transplant. 2000; 26(7):717-22. doi: 10.1038/sj.bmt.1702609. PMID: 11042651
22. Hwang SB, Lee HY, Kim HY, Lee ES, Bae JW. Life-threatening acute hyponatremia with generalized seizure induced by low-dose cyclophosphamide in a patient with breast cancer. J Breast Cancer. 2011; 14(4):345-348. doi: 10.4048/jbc.2011.14.4.345. PMCID: PMC3268935
23. Kawakami K, Ito R, Kageyama Y, Nagaharu K, Yamaguchi T, Ito N. Superior sagittal sinus thrombosis after intrathecal chemotherapy and intravenous high-dose cytarabine in an acute myeloid leukemia case with t(8;21)(q22;q22). Rinsho Ketsueki. 2016; 57(4):477-482 (Japanese). doi: 10.11406/rinketsu.57.477. PMID: 27169454
24. Bauwens D, Hantson P, Laterre PF, et al. Recurrent seizure and sustained encephalopathy associated with dimethylsulfoxide-preserved stem cell infusion. Leukemia & Lymphoma. 2005; 46(11):1671-1674. doi: 10.1080/10428190500235611
25. Maral S, Albayrak M, Pala C, Yildiz A, Sahin O, Ozturk HB. Dimethyl sulfoxide-induced tonic-clonic seizure and cardiac arrest during infusion of autologous peripheral blood stem cells. Cell Tissue Bank. 2018;19(4):831-832. doi: 10.1007/s10561-018-9718-x
26. Hequet O, Dumontet C, El Jaafari-Corbin A. et al. Epileptic seizures after autologous peripheral blood progenitor infusion in a patient treated with high-dose chemotherapy for myeloma. Bone Marrow Transplant. 2002; 29(6):544. doi: 10.1038/sj.bmt.1703383. PMID: 11960281
27. Inaba H, Khan RB, Laningham FH, Crews KR, Pui CH, Daw NC. Clinical and radiological characteristics of methotrexate-induced acute encephalopathy in pediatric patients with cancer. Ann Oncol. 2008; 19(1):178-184. doi: 10.1093/annonc/mdm466. PMID: 17947226

28. Rao RD, Swanson JW, Dejesus RS, Hunt CH, Tefferi A. Methotrexate induced seizures associated with acute reversible magnetic resonance imaging (MRI) changes in a patient with acute lymphoblastic leukemia. Leuk Lymphoma. 2002; 43(6):1333-1336. doi: 10.1080/10428190290026402. PMID: 12153004
29. Abraham P, Longardner K, Chen P, Huisa B, Handwerker J. Case 279: Central-variant posterior reversible encephalopathy syndrome. Radiology. 2020; 296(1): 239-243. doi: 10.1148/radiol.2020181547. PMID: 32539624; PMCID: PMC7325905
30. Teimouri A, Ahmadi SR, AnavriArdakani S, Foroughian M. Cyclosporine-a-based immunosuppressive therapy-induced neurotoxicity: A case report. Open Access Emerg Med. 2020; 12:93-97. doi: 10.2147/OAEM.S241501. PMID: 32431553
31. He W, Chen J, Wang YY, Zhang MN, et. al. Sirolimus improves seizure control in pediatric patients with tuberous sclerosis: A prospective cohort study. Seizure. 2020 ; 79:20-26. doi: 10.1016/j.seizure.2020.03.018
32. Xie M, Rao W, Sun LY, Zhu ZJ, Deng YL, Shen ZY, Jia JD. Tacrolimus-related seizure after pediatric liver transplantation--a single-center experience. Pediatr Transplant. 2014; 18(1):58-63. doi: 10.1111/petr.12198. PMID: 24283660
33. Sevmis S, Karakayali H, Emiroglu R, Akkoc H, Haberal M. Tacrolimus-related seizure in the early postoperative period after liver transplantation. Transplant Proc. 2007; 39(4):1211-1213. doi: 10.1016/j.transproceed.2007.02.049. PMID: 17524935
34. Vesole AS, Nagahama Y, Granner MA, Howard MA, Kawasaki H, Dlouhy BJ. Drug-resistant epilepsy development following stem cell transplant and cyclosporine neurotoxicity induced seizures: Case report in an adult and analysis of reported cases in the literature. Epilepsy Behav Case Rep. 2018, Feb 8;10:8-13. doi: 10.1016/j.ebcr.2018.01.002. PMID: 30062084
35. Kadish NE, Riedel C, Stephani U, Wiegand G. Developmental outcomes in children/adolescents and one adult with tuberous sclerosis complex (TSC) and refractory epilepsy treated with everolimus. Epilepsy Behav. 2020; 111:107182. doi: 10.1016/j.yebeh.2020.107182. PMID: 32535369
36. Hung JJ, Huang JL. Etanercept therapy in children with juvenile rheumatoid arthritis. J Microbiol Immunol Infect. 2005; 38(6):444-446. PMID: 16341346
37. Cannon JP, Lee TA, Clark NM, Setlak P, Grim SA. The risk of seizures among the carbapenems: a meta-analysis. J Antimicrob Chemother. 2014;69(8):2043-2055. doi: 10.1093/jac/dku111
38. Conley TE, Mohiuddin A, Naz N. Severe co-trimoxazole-induced hypoglycaemia in a patient with microscopic polyangiitis. BMJ Case Rep. 2017;2017:bcr2016218976. Published 2017 Mar 16. doi: 10.1136/bcr-2016-218976
39. Balkan II, Delil S, Karabacak ER, Yemisen M, Ozaras R, Yeni N. Linezolide -induced complex partial seizure in a patient without epilepsy. Int J Infect Dis. 2015; 35:120. doi: 10.1016/j.ijid.2015.05.007
40. Lin CS, Cheng CJ, Chou CH, Lin SH. Piperacillin/tazobactam-induced seizure rapidly reversed by high flux hemodialysis in a patient on peritoneal dialysis. Am J Med Sci. 2007; 333(3):181-184. doi: 10.1097/MAJ.0b013e31803195e7. PMID: 17496739
41. Chow KM, Szeto CC, Hui AC, Wong TY, Li PK. Retrospective review of neurotoxicity induced by cefepime and ceftazidime. Pharmacotherapy. 2003; 23(3):369-373. doi: 10.1592/phco.23.3.369.32100. PMID: 12627936
42. Grill MF, Maganti R. Cephalosporin-induced neurotoxicity: clinical manifestations, potential pathogenic mechanisms, and the role of electroencephalographic monitoring. Ann Pharmacother. 2008; 42(12):1843-1850. doi: 10.1345/aph.1L307. PMID: 19033476
43. Agbaht K, Bitik B, Piskinpasa S, Bayraktar M, Topeli A. Ciprofloxacin-associated seizures in a patient with underlying thyrotoxicosis: case report and literature review. Int J Clin Pharmacol Therapeutics. 2009; 47(5):303-310. doi: 10.5414/cpp47303
44. Barton TL, Roush MK, Dever LL. Seizures associated with ganciclovir therapy. Pharmacotherapy. 1992;12(5):413-415. PMID: 1331995
45. Foroughinia F, Baniasadi S, Seifi S, Fahimi F. Vincristine-induced seizure potentiated by itraconazole following RCHOP chemotherapy for diffuse large B-cell lymphoma. Curr Drug Saf. 2012; 7(5):372-374. doi: 10.2174/157488612805076633. PMID: 23320431
46. Hamdy DA, El-Geed H, El-Salem S, Zaidan M. Posaconazole-vincristine coadministration triggers seizure in a young female adult: a case report. Case Rep Hematol. 2012; 2012:343742. doi: 10.1155/2012/343742
47. Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia. 2010; 51(4):671-675. doi: 10.1111/j.1528-1167.2009.02285.x
48. Common Terminology Criteria for Adverse Events (CTCAE): https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Access date: 27.10.2020.
49. Saner F, Gu Y, Minouchehr S, et al. Neurological complications after cadaveric and living donor liver transplantation. J Neurol. 2006; 253(5):612-617. doi: 10.1007/s00415-006-0069-3
50. Forgacs B, Merhav HJ, Lappin J, Mieles L. Successful conversion to rapamycin for calcineurin inhibitor-related neurotoxicity following liver transplantation. Transplant Proc. 2005; 37(4):1912-1914. doi: 10.1016/j.transproceed.2005.02.101. PMID: 15919502
51. Shuto H, Kataoka Y, Fujisaki K, et al. Inhibition of GABA system involved in cyclosporine-induced convulsions. Life Sci. 1999; 65(9):879-887. doi: 10.1016/s0024-3205(99)00318-5
52. Klawitter J, Gottschalk S, Hainz C, et al. Immunosuppressant neurotoxicity in rat brain models: oxidative stress and cellular metabolism. Chem Res Toxicol. 2010; 23(3):608-619. doi: 10.1021/tx900351q
53. Katsarou AM, Moshé SL, Galanopoulou AS. Interneuronopathies and their role in early life epilepsies and neurodevelopmental disorders. Epilepsia Open. 2017; 2(3):284-306. doi: 10.1002/epi4.12062. PMCID: PMC5650248

54. Wong M, Yamada KA. Cyclosporine induces epileptiform activity in an in vitro seizure model. Epilepsia. 2000; 41(3):271-276. doi: 10.1111/j.1528-1157.2000.tb00155.x. PMID: 10714397
55. Li Y, Wang H, Han D, et al. Acute symptomatic seizure due to tacrolimus-related encephalopathy after liver transplantation: two case reports. J Int Med Res. 2019; 47(12):6397-6403. doi: 10.1177/0300060519883750. PMID: 31709865
56. Savolainen H, Tenhunen R. Inhibition of heme synthase in brain and liver by low-level peroral sulfite exposure. Res Commun Chem Pathol Pharmacol. 1982; 36(3):511-4. PMID: 7122992
57. Chen-Plotkin AS, Vossel KA, Samuels MA, Chen MH. Encephalopathy, stroke, and myocardial infarction with DMSO use in stem cell transplantation. Neurology. 2007; 68(11):859-861. doi: 10.1212/01.wnl.0000256716.04218.5b
58. Ruiz-Delgado GJ, Mancías-Guerra C, Tamez-Gómez EL, et al. Dimethyl sulfoxide-induced toxicity in cord blood stem cell transplantation: report of three cases and review of the literature. Acta Haematol. 2009; 122(1):1-5. doi: 10.1159/000227267
59. Pillinger KE, Bouchard J, Withers ST, et al. Inpatient antibiotic stewardship interventions in the adult oncology and hematopoietic stem cell transplant population: A review of the literature. Ann Pharmacother. 2020; 54(6):594-610. doi: 10.1177/1060028019890886. PMID: 31771337
60. Rival M, Chetioui A, Tailland M, Renard D. Linezolid-induced status epilepticus. Acta Neurol Belg. 2020. doi: 10.1007/s13760-020-01333-2
61. Bora I, Demir AB, Uzun P. Nonconvulsive status epilepticus cases arising in connection with cephalosporins. Epilepsy Behav Case Rep. 2016; 6:23-27. doi: 10.1016/j.ebcr.2016.04.005
62. Meyer MA. Myoclonic jerks secondary to piperacillin and nafcillin. Neurol Int. 2014;6(2):5349. doi: 10.4081/ni.2014.5349
63. Jang JH, Song KS, Bang JS, Oh CW, Kwon OK, Chung YS. What should be considered to cause the early post-craniotomy seizure: Antibiotics (Cefazolin) irrigation. J Korean Neurosurg Soc. 2015; 58(5):462-466. doi: 10.3340/jkns.2015.58.5.462
64. McCune JS, Wang T, Bo-Subait K, et al. Association of antiepileptic medications with outcomes after allogeneic hematopoietic cell transplantation with busulfan/cyclophosphamide conditioning. Biol Blood Marrow Transplant. 2019; 25(7):1424-1431. doi: 10.1016/j.bbmt.2019.03.001. PMID: 30871976; PMCID: PMC6615968
65. Nardone R, Brigo F, Trinka E. Acute symptomatic seizures caused by electrolyte disturbances. J Clin Neurol. 2016; 12(1):21-33. doi: 10.3988/jcn.2016.12.1.21. PMID: 26754778
66. Schwartzkroin PA, Baraban SC, Hochman DW. Osmolarity, ionic flux, and changes in brain excitability. Epilepsy Res. 1998; 32(1-2):275-285. doi: 10.1016/s0920-1211(98)00058-8
67. Filippatos TD, Milionis HJ, Elisaf MS. Alterations in electrolyte equilibrium in patients with acute leukemia. Eur J Haematol. 2005; 75(6):449-460. doi: 10.1111/j.1600-0609.2005.00547.x
68. Anandan A, Kolk M, Ferrari N, et al. Serum electrolyte dynamics in multiple myeloma patients undergoing autologous haematopoietic stem cell transplantation. Nephrology (Carlton). 2020; 25(6):450-456. doi: 10.1111/nep.13712
69. Milionis HJ, Bourantas CL, Siamopoulos KC, Elisaf MS. Acid-base and electrolyte abnormalities in patients with acute leukemia. Am J Hematol. 1999; 62(4):201-207. doi: 10.1002/(SICI)1096-8652(199912)62:4<201::AID-AJH1>3.0.CO;2-1. PMID: 10589074
70. Philibert D, Desmeules S, Filion A, Poirier M, Agharazii M. Incidence and severity of early electrolyte abnormalities following autologous haematopoietic stem cell transplantation. Nephrol Dial Transplant. 2008;23(1):359-363. doi: 10.1093/ndt/gfm571
71. Van Amelsvoort T, Bakshi R, Devaux CB, Schwabe S. Hyponatremia associated with carbamazepine and oxcarbazepine therapy: a review. Epilepsia. 1994; 35(1): 181-188. doi: 10.1111/j.1528-1157.1994.tb02930.x. PMID: 8112243
72. de Leeuw DC, Kooter AJ. Transient seizure-induced sodium increase camouflaging a symptomatic hyponatremia. BMJ Case Rep. 2020; 13(1):e229328. doi: 10.1136/bcr-2019-229328
73. Pilato F, Distefano M, Calandrelli R Posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome: Clinical and radiological considerations. Front Neurol. 2020; 11:34. doi: 10.3389/fneur.2020.00034. PMID: 32117007
74. Chen Q, Zhao X, Fu HX, et al. Posterior reversible encephalopathy syndrome (PRES) after haploidentical haematopoietic stem cell transplantation: incidence, risk factors and outcomes. BoneMarrowTransplant. 2020. doi: 10.1038/s41409-020-0894-5
75. Datar S, Singh T, Rabinstein AA, et al. Long-term risk of seizures and epilepsy in patients with posterior reversible encephalopathy syndrome. Epilepsia. 2015;56(4):564-568. doi: 10.1111/epi.12933
76. Hammerstrom AE, Howell J, Gulbis A, et al. Tacrolimus-associated posterior reversible encephalopathy syndrome in hematopoietic allogeneic stem cell transplantation. Am J Hematol. 2013; 88(4):301-305. doi: 10.1002/ajh.23402
77. Gaziev J, Marziali S, Paciaroni K, et al. Posterior reversible encephalopathy syndrome after hematopoietic cell transplantation in children with hemoglobinopathies. Biol Blood Marrow Transpl. 2017; 23:1531-1540. doi: 10.1016/j.bbmt.2017.05.033
78. April D, Lall N, Steven A. Stroke-like migraine attacks after radiation therapy syndrome. Ochsner J. 2020; 20(1):6-9. doi: 10.31486/toj.19.0090
79. Kerklaan JP, Lycklama á Nijeholt GJ, et al. SMART syndrome: a late reversible complication after radiation therapy for brain tumours. J Neurol. 2011; 258(6):1098-1104. doi: 10.1007/s00415-010-5892-x

80. Farid K, Meissner WG, Samier-Foubert A, Barret O, Menegon P, Rouanet F, et al. Normal cerebrovascular reactivity in stroke-like migraine attacks after radiation therapy syndrome. Clin Nucl Med. 2010; 35(8):583-585. doi: 10.1097/RLU.0b013e3181e4db6f
81. Suarez Montero JC, Caballero Gonzalez AC, Martín Aguilar L, Mancebo Cortés J. Immune effector cell-associated neurotoxicity syndrome: A therapeutic approach in the critically ill. Med Intensiva. 2020: S0210-5691(20)30244-8. (Spanish). doi: 10.1016/j.medin.2020.06.014. PMID: 32873409
82. Perrin P, Collongues N, Baloglu S, Bedo D, Bassand X, Lavaux T, et al. Cytokine release syndrome-associated encephalopathy in patients with COVID-19. Eur J Neurol. 2021; 28(1):248-258. doi: 10.1111/ene.14491. PMID: 32853434
83. Garcia Borrega J, Gödel P, Rüger MA, Onur ÖA, Shimabukuro-Vornhagen A, Kochanek M, Böll B. In the eye of the storm: Immune-mediated toxicities associated with CAR-T cell therapy. Hemasphere. 2019; 3(2):e191. doi: 10.1097/HS9.0000000000000191
84. Gust J, Finney OC, Li D, Brakke HM, Hicks RM, Futrell RB, et al. Glial injury in neurotoxicity after pediatric CD19-directed chimeric antigen receptor T cell therapy. Ann Neurol. 2019; 86(1):42-54. doi: 10.1002/ana.25502. PMID: 31074527
85. Gust J, Hay KA, Hanafi LA, Li D, Myerson D, Gonzalez-Cuyar LF, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. Cancer Discov. 2017; 7(12):1404-1419. doi: 10.1158/2159-8290.CD-17-0698. PMID: 29025771
86. Zheng W. Neurotoxicology of the brain barrier system: new implications. J Toxicol Clin Toxicol. 2001;39(7):711-719. doi: 10.1081/clt-100108512
87. Martell RW, Sher C, Jacobs P, Monteagudo F. High-dose busulfan and myoclonic epilepsy. Ann Intern Med. 1987;106(1):173. doi: 10.7326/0003-4819-106-1-173_1
88. Janssen S, Bloem BR, van de Warrenburg BP. The clinical heterogeneity of drug-induced myoclonus: an illustrated review. J Neurol. 2017; 264(8):1559-1566. doi: 10.1007/s00415-016-8357-z
89. Dowling MR, Li S, Dey BR, McAfee SL, Hock HR, Spitzer TR, Chen YB, Ballen KK. Neurologic complications after allogeneic hematopoietic stem cell transplantation: risk factors and impact. Bone Marrow Transplant. 2018; 53(2):199-206. doi: 10.1038/bmt.2017.239
90. Hamidieh AA, Hamedani R, Hadjibabaie M, Amini M, Sadrai S, Ghavamzadeh A. Oral lorazepam prevents seizure during high-dose busulfan in children undergoing hematopoietic stem cell transplantation: a prospective study. Pediatr Hematol Oncol. 2010; 27(7):529-533. doi: 10.3109/08880018.2010.496895
91. Ruiz-Argüelles GJ, Gomez-Almaguer D, Steensma DP. Outdated dogma? Busulfan, seizure prophylaxis, and stem cell allografting. Am J Hematol. 2012;87(9):941. doi: 10.1002/ajh.23270
92. Diaz-Carrasco MS, Olmos R, Blanquer M, Velasco J, Sánchez-Salinas A, Moraleda JM. Clonazepam for seizure prophylaxis in adult patients treated with high dose busulfan. Int J Clin Pharm. 2013; 35(3):339-343. doi: 10.1007/s11096-013-9768-x. PMID: 23575621
93. Chan KW, Mullen CA, Worth LL, Choroszy M, Koontz S, Tran H, Slopis J. Lorazepam for seizure prophylaxis during high-dose busulfan administration. Bone Marrow Transplant. 2002; 29(12):963-965. doi: 10.1038/sj.bmt.1703593
94. Hassan M, Oberg G, Björkholm M, Wallin I, Lindgren M. Influence of prophylactic anticonvulsant therapy on high-dose busulphan kinetics. Cancer Chemother Pharmacol. 1993;33(3):18118-6. doi: 10.1007/BF00686213. PMID: 8269597
95. Carreras E, Cahn JY, Puozzo C, Kröger N, Sanz G, Buzyn A, Bacigalupo A, Vernant JP. Influence on Busilvex pharmacokinetics of clonazepam compared to previous phenytoin historical data. Anticancer Res. 2010; 30(7):2977-2984. PMID: 20683042
96. Chaguaceda C, Aguilera-Jiménez V, Gutierrez G, Roura J, Riu G. Oral levetiracetam for prevention of busulfan-induced seizures in adult hematopoietic cell transplant. Int J ClinPharm. 2020;42(2):351-354. doi: 10.1007/s11096-020-00977-7
97. Floeter AE, McCune JS. Levetiracetam for the prevention of busulfan-induced seizures in pediatric hematopoietic cell transplantation recipients. J Oncol Pharm Pract. 2017; 23(5):344-349. doi: 10.1177/1078155216651128
98. Eberly AL, Anderson GD, Bubalo JS, McCune JS. Optimal prevention of seizures induced by high-dose busulfan. Pharmacotherapy. 2008;28(12):1502-1510. doi: 10.1592/phco.28.12.1502
99. Marcus RE, Goldman JM. Convulsions due to high-dose busulphan. Lancet. 1984; 2(8417-8418):1463. doi: 10.1016/s0140-6736(84)91649-0
100. Vassal G, Deroussent A, Hartmann O, et al. Dose-dependent neurotoxicity of high-dose busulfan in children: a clinical and pharmacological study. Cancer Res. 1990; 50(19):6203-6207. PMID: 2400986
101. Woodward S. Management of faecal incontinence in graft-versus-host disease. Br J Nurs. 2012;21(2):84-88. doi: 10.12968/bjon.2012.21.2.84

Остро возникшие симптоматические эпилептические приступы как осложнение трансплантации гемопоэтических стволовых клеток пациентов с лейкозом: обзор литературы

Алексей Ю. Полушин, Ярослав Б. Скиба, Михаил О. Садовских, Мария Д. Владовская, Александр Д. Кулагин

Первый Санкт-Петербургский государственный медицинский университет им. акад. И. П. Павлова, Санкт-Петербург, Россия

РЕЗЮМЕ

Остро возникшие симптоматические эпилептические приступы являются вероятным осложнением трансплантации гемопоэтических стволовых клеток у пациентов с лейкозом. Развитие данного осложнения может наблюдаться на этапе кондиционирования, в раннем и позднем посттрансплантационном периодах. При этом этиологические факторы, приводящие к развитию данного осложнения, отличаются от таковых в общей популяции, а значимость каждого из них различна в зависимости от сроков после трансплантации. В статье проанализированы данные литературы, посвященные роли лекарственных препаратов, синдрома выброса цитокинов, метаболических нарушений и инфекционных осложнений, а также структурной патологии вещества головного мозга в развитии симптоматических эпилептических приступов у пациентов с лейкозом. Авторами рассмотрены клинические особенности симптоматических эпилептических приступов при проведении трансплантации гемопоэтических стволовых клеток, оценено возможное прогностическое значение их развития у пациентов.

Ключевые слова: лейкоз, эпилептический приступ, генерализованные тонико-клонические судороги, синдром выброса цитокинов, трансплантация, гипонатриемия, гемопоэтические стволовые клетки, бусульфан.