Neuropathy and Myopathy in Patients with Graft-Versus-Host Disease Treatment and Diagnostic Algorithm: Review of the Literature

A. Straukienė*
K. Andrėkutė**
V. Pečeliūnas**
R. Meškauskas***
J. Wanschitz****
W. Löscher****
V. Budrys*

*Clinics of Neurology and Neurosurgery, Faculty of Medicine,Vilnius University; Center of Neurology, Vilnius University Hospital Santariskiu Clinics, Lithuania

**Center of Hematology, Oncology and Transfusion Medicine, Vilnius University Hospital Santariskiu Clinics, Lithuania

***Lithuanian National Center of Pathology, Lithuania

****Electrophysiological and Neuromuscular Unit, Innsbruck University Hospital, Austria

Summary. Vilnius University Hospital Center of Hematology, Oncology and Transfusion Medicine (HOTC) performs about 100–120 hematopoietic stem cell transplantations per year (HSCT). According to the number of hematopoietic stem cell transplantations Vilnius HOTC is very close to the number of patients at one of the biggest European Hematology and Bone Marrow Transplantation center at Innsbruck University Hospital in Austria. Hematopoietic stem cell transplantation (HSCT) is a method of treatment when potentially neurotoxic medications presse immune system and destroy tumor cells. Most frequently such as oncohematology diseases, aplastic anemia or metabolic disorders are treated. Nowadays the urgent topic that has been discussed is neurological complications after HSCT. It occurs from 37% to 91% and is the main cause of death accounting from 6% to 26%. The circumstance aggravating the overall condition of patients is autoimmune system activation against the transplantant. It is called graft-versus-host disease (GVHD). When immune system activation occurs more than 100 days after transplantation it is called chronic GVHD. Most often GVHD damages gastrointestinal tract, liver, skin, and lungs. So long there are few case reports of GVHD and neurological complications. It results from masked clinics and complicated diagnostics due to continuous immunosuppression and neurotoxic impact of chemotherapy.

This article focuses on the peripheral nervous system damage (chronic inflammatory demyelinating polyradiculoneuropathy, Guillain-Barre syndrome), neuromuscular disease (myasthenia gravis) and myopathy after hematopoietic stem cell transplantation and GVHD. Furthermore, we present Rituximab treatment recommendations to glucocorticoids refractory GVHD forms. To conclude, we recommend algorithms for diagnosis and treatment of possible peripheral nervous system and muscular diseases and GVHD.

Keywords: hematopoietic stem cell transplantation, immunosuppression, graft-versus-host disease, Guillain–Barre syndrome, myasthenia, rituximab.

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is an intractable complication associated with considerable morbidity and being a leading cause of non-relapse mortality: the average mortality is 26%. Though several investigational treatment options showed preliminary favourable outcomes including treatment with Rituximab, plasmopheresis, Sirolimus [1–3], as initially defined, resembled an autoimmune disorder occurring 100 days after allogeneic transplantation. The arbitrary day of onset, however, may not be as crucial in separating acute from chronic GVHD; rather, these two syndromes appear to result from different mechanisms [4, 5]. cGVHD is known to involve skin, gut, liver. Targeting of other organ systems is described; however overlaping symptoms caused by infections, autoimmune manifestations, drugs make the diagnosis challenging.

Address:

Center of Neurology,
Vilnius University Hospital Santariskiu Clinics,
Santariškių str. 2, LT-08661 Vilnius, Lithuania
Tel. (3705) 2365220, e-mail: valma@takas.lt

Research in the area of neurologic complications and its association with GVHD is limited with regard to allogeneic hematopoietic stem cell transplantation (allo-HSCT). Most studies have been retrospective [6–11]. Prospective evaluation of this complication has been rare [12, 13]. The incidence of neurologic complications has varied from 37% to 91%, and such complications have been the cause of death in 6% to 26% of patients [6].

Neurologic symptoms and signs which were mild and sub-acute and predominantly affected the peripheral nervous system after HSCT have been reported in 57% of the patients. Signs indicated axonal sensory-motor polyneuropathy and proximal muscular atrophy. The risk factors of neurologic complications were, acute GVHD, chronic GVHD, liver dysfunction, total body irradiation, use of steroids more than 3 months, previous chemotherapy cycles [12]. In those patients who have got mild sensory polyneuropathy because of cycles of chemotheraphy before HSCT, it worsens after HSCT [14]. Neuromuscular system involvement in GVHD is under attention in the past decade [15]. Peripheral neuropathy has also been associated with either acute or chronic GVHD after allogeneic HSCT. Most cases developed neuropathy as an acute Guillain–Barré syndrome (GBS) or chronic recurrent form as chronic inflammatory demyelinating polyneuropathy (CDIP). Although, in a setting of stable GVHD, all peripheral nervous system damages could be interpreted as GVHD induced neuropathy or myopathy. There are some reports on polyneuropathy in patients with GVHD after bone marrow transplantation.

IMMUNE-MEDIATED NEUROPATHIES AND MYOPATHIES

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

CIDP is an unusual, but important complication of HSCT [16, 17]. Inflammatory demyelinating polyradiculoneuropathy (CIDP) as a manifestation of GVHD was first reported in 1991 and was followed by eight further cases in the following decade. Authors Werneck et all [19] have described CIDP manifestation in chronic Graft-versus-host disease. CIDP is a clinical syndrome based on a physiological and pathological concept as followed: (1) clinical features of chronic progressive or relapsing and remitting, symmetrical, sensory and motor polyradiculoneuropathy causing weakness of proximal and distal muscles; (2) CSF protein concentration is almost always increased; (3) electrophysiological evidence of demyelination is required for the diagnosis and axonal degeneration can occurs in evolution; (4) histological examination reveals demyelination with variable inflammatory infiltrates. The CIDP also occurs after HSCT as a chronic progressive or relapsing and remitting CIDP [15, 19].

Guillain–Barre syndrome (GBS)

Guillain–Barre syndrome is a rare complication following hematopoietic stem cell transplantation (HSCT). Only a few cases of GBS during acute graft-versus-host disease (acute GVHD) have been reported and its pathogenesis is unclear. GBS in the early period post HSCT has been attributed to the conditioning regimen, particularly cytosine arabinoside [20]. In contrast, the etiology of GBS in the late HSCT period remains unknown [21]. Some reports suggest an association with antecedent infections such as Campylobacter pylori and cytomegalovirus (CMV). GBS is characterized by rapidly evolving limb weakness, loss of deep tendon reflexes, absent or mild sensory deficits, and variable autonomic dysfunction. Weakness can develop acutely (days) or sub-acutely (up to 4 weeks), and it may progress with eventual resolution of paralysis [22, 23] (table 1).

Myasthenia gravis

Myasthenia gravis is an autoimmune disease rarely diagnosed following HSCT. It may be a part of the spectrum of chronic graft-versus-host disease (GVHD) [24] and is associated with discontinuation of immunosuppressants [25]. Muscle weakness often involves the ocular muscles, bulbar muscles and muscles innervated by other facial nerves. It can be generalized and might involve the proximal limb muscles as well. The diagnosis is made clinically and supported by electro-diagnostic testing, elevated titers of anti-AChR antibodies, and improvement in strength with anticholinesterase therapy (table 2).

The analysis of reports supports the idea that GVHD is a multi systemic organ system disease; obviously the peripheral nervous system could also be involved in the pathogenesis of GVHD.

Myositis

Myositis as a complication of cGVHD has been reported in up to 7.6% of patients [4]. Chronic GVHD-related polymyositis has been reported, usually with other manifestations of GVHD. Previous studies have described a heterogeneous group of myositis-associated chronicle GVHD patients, most with either nonspecific muscle biopsy findings [26, 27], or without muscle biopsy analysis [28, 29]. Muscle may be a target tissue for chronic GVHD. Among 1859 individuals who developed chronic GVHD, 12 developed myositis. It was first identified between 7 weeks and 5 months after transplantation. In histopathology, electromyography, laboratory values and response to immunosuppressive therapy, the cases resembled idiopathic polymyositis. Autoantibodies were found in eight cases [30]. The predominant clinical picture described is one of proximal weakness and myalgia, often responding to corticosteroids or other immunosuppressive treatment. Distal weakness in patients following HSCT might also reflect the presence of a GVHD-associated polyneuropathy or the toxic effects of chemotherapeutic agents [19].

Table 1. **Reported cases of CIDP and GBS after HSCT**

Author	Years	Age / Sex	Underlying disorder	Latency*	Neurological toxicity	CSF protein	Histology	Treatment	Out-come
Amato et al. (Amato, 1993)	1993	31/M	CML	6 months	CIDP	NP	No	PSL+AZP+CS+IvIg	R
		44/M	CML	8 months	CIDP	?	No	PP+PSL+CS	R
		29/M	AA	2 weeks	CIDP	NP	No	PSL+CS+IvIg	R
		43/M	NHL	1 month	CIDP	?	No	PP+PSL	R
Adams et al. (Adams, 1995)	1995	5/F	MOP	4 years	CIDP	NP	No	P+CS	R
Griggs et al. (Griggs, 1997)	1997	42/M	NHL	3 years	CIDP	?	No	PP	R
Nagashima et al. (Nagashima, 2002)	2002	32/M	NHL	5 years	CIDP	NL	The sural nerve showed a loss of myelinated nerve fibers with epineurial fibrosis and rare occurrence of T cells, but without obvious vasculitic changes.	MPS	PR
Openshaw et al. (Openshaw, 1991)	1991	36/M	CML	7 days	CIDP	?	Sections of multiple peripheral nerves sampled post mortem revealed prominent demyelination with heavy infiltration of macrophages and lymphocytes. Immuno-histochemical studies demonstrated that most of the lymphocytes were of the CD8+, cytotoxic/suppressor cell class and that many of the Schwann cells expressed class II (HLA-DR) antigen.	P+CP+PP+IvIg	D
		21/M	HL	16 days	CIDP	?	No	P+CP+PP+IvIg	D
Peter et al. (Peters, 2005)	2005	62/M	MM	1 month	CIDP	NP	No	NP	R
Lorenzoni et al. (Lorenzoni, 2007)	2007	17/F	AML	10 months	CIDP	?	The nerve biopsy had mild inflammatory perivascular lymphomononuclear infiltration in the endoneurium and epineurium, a reduction in the number of large myelinized fibers in some sectors of the fascicles, asymmetrical axonal degeneration within fascicles, occasional presence of myelin ovoid, and compact and disarranged myelin sheath in most of the material.	IvIg+PP+P+MM	R
Wada et al. (Wada, 2008)	2008	54/M	ALL	1 year	CIDP	?	Peroneal nerve biopsy revealed demyelination.	IvIg	R
Gonzales et al. (MI González, 2000)	2000	25/?	CML	7 days	GBS (toxoplasmosis)	NL	Axonal degeneration of nerve roots compatible with the axonal form of GBS.	?	D
Suzuki et al. (S Suzuki, 2007)	2007	58/F	ALL	6 months	GBS	?	No	IvIg+PSL+T	D
Rodriguez et al. (Krance RA, 2002)	2002	16/M	T cell leukemia	6 days	GBS	?	No	IvIg	D
		17/M	T cell lymphoma	5 days	GBS	?	No	IvIg	D
		18/M	ALL	2 days	GBS	?	No	IvIg	D
Hernández-Boluda et al. (J.-C. Hernández-Boluda, 2005)	2005	23/?	AML	?	GBS	?	?	?	D

Table 1. **Reported cases of CIDP and GBS after HSCT** *(cont.)*

Author	Years	Age / Sex	Underlying disorder	Latency*	Neurological toxicity	CSF protein	Histology	Treatment	Outcome
Khan et al. (B Khan, 2005)	2005	?	Aplastic anaemia	?	GBS	?	?	IvIg	R
Zhang et al. (L Zhang, 2008)	2008	?	?	?	GBS	?	?	?	?
		?	?	?	GBS	?	?	?	?
Janssen et al. (JJ Janssen, 1999)	1999	?	CML	?	GBS	?	?	?	?
Mudad et al. (R Mudad, 1995)	1995	44/F	Breast cancer	2 days	GBS	?	?	PP	R
Myers et al. (SE Myers, 1994)	1994	?/F	Breast cancer	?	GBD	?	?	PP	R
		?/F	Breast cancer	?	GBS	?	?	?	D
Perry et al. (A Perry, 1994)	1994	?/?	CML	4 month	GBS	?	?	PP	R
Wen et al. (PY Wen 1997)	1997	?/?	?	?	GBS	?	?	?	?
		?/?	?	?	GBS	?	?	?	?
		?/?	?	?	GBS	?	?	?	?
		?/?	?	?	GBS	?	?	?	?
Nasilowska-Adamska et al. (B Nasilowska-Adamska 2006)	2006	40/F	CML	?	GBS	?	?	?	?
Thöne et al. (J Thöne 2010)	2010	?/F	?	?	GBS	?	?	IvIg+PP	?

*Interval after HSCT; M – male; F – female; CML – chronic myeloid leukemia; HL – Hodgkin lymphoma; AA – aplastic anemia; NHL – non-Hodgkin lymphoma; MOP – malignant osteopetrosis; MM – multiple myeloma; AML – acute myeloid leukemia; ? – increased; NP – not performed; NL – normal; P – prednisone; CP – cyclophosphamide; PP – plasmapheresis; PSL – prednisolone; AZP – azathioprin; CS – cyclosporine; IvIg – intravenous immunoglobulin; MPS – methylprednisolone; MM – mofetil mycophenolate, T – tacrolimus, R – recovery, PR – partial recovery, D – death.

Table 2. **Reported cases of Myastenia gravis after HSCT**

Author	Mackey (CR)	Zaja F. R., 1995	Shimoda K, 1994	Melms A, 1992	Atkinson K, 1989	Smith CIE, 1989	Seely E, 1984	Bolger GB S. K., 1986	Bolger GB S. K., 1986	Rainer Storb 1986	Grau JM C. J., 1990
Disease	AML	AML	CML	AA	AA	AA	AA	AA	AA	NHL	T- ALL
Sex Mismatch	-	+	-	+	+	+	+	+	-	+	+
Chronic GVHD	+	+	+	+	+	+	+	+	+	+	+
Sicca	+	+	+	-	+		+	+		+
Liver	+	-	+	-	+		+	+		+
Skin	+	+	+	-	+		+	+		+
Lung	-	-	-	+	-		-	-		-
Oral	-	+	-	+	-		-	-		-
Time of MG after HSCT (months)	100	46	29	60	19	27	35	33	25	26	46
Anti-AChr antibody elevation	+	+	+	+	+	+	+	+	+	+	+
Thymoma	no	no	no	NR	no	no	no	no	no	NR	no
Accociated with imunosuppresion discontinuation	+	+	+	+	+	+	NR	+	+	NR	+

AML – acute myelogenous leukemia; ALL – acute lymphoblastic leukemia; CML – chronic myelogenous leukemia; NHL – non-Hodgkin's lymphoma; AA – aplastic anemia; NR – not reported; "+" present; "–"absent. Anti-AChr – anticholinesterase receptor.

HISTOLOGY

All consideration whether CIDP manifests as an independent disease after HSCT or it occurs in terms of GVHD could be defined by histological confirmation which can be obtained in nerve or skin biopsy. The characteristic lesions of CIDP consist of patchy regions of demyelination and edema with variable inflammatory infiltrates, a reduction in the number of large myelinated fibers in some sectors of the fascicles, asymmetrical axonal degeneration within fascicles, occasional presence of myelin ovoid, and compact and disarranged myelin sheath in most of the material [31]. The inflammatory infiltrates are found in both the endoneurium and the epineurium but, in contrast to vasculitic neuropathy, are more abundant in the endoneurium made of mononuclear cells, mainly lymphocytes and macrophages cells. The histological analysis of the nerve showed perivascular inflammatory cells in 54.5% of the patients with CIDP [32].

Histopathological studies were performed in only three cases and immunohistochemical analysis was described in a single report and these have shown demyelization and vasculitis of the peripheral nerves. Biopsies taken from the left quadriceps femoris muscle, skin and sural nerve were fixed in formalin, embedded in paraffin and stained. For immunohistochemistry the sections were also stained for several lymphocyte markers including CD4, CD8 and UCHL-1, CD45RO, CD3 and CD68. In the muscle T-cell infiltration was detected around atrophied myocytes. The sural nerve showed a decreased number of myelinated fibers and marked nerve fiber depletion replaced by fibrosis and a slight intimal thickening with medial fibrosis of an accompanying arteriole [15]. There are no reports whether inflammatory infiltrate could be donors T, B lymphocytes, which could improve the GVHD and peripheral nervous system damage or myopathy diagnosis. Nevertheless, specific muscle findings can be similar to nerve findings varying according to the time and the severity of the disease [18]. American academy of neurology has reported evidence- based guidelines regarding the role of nerve biopsy and skin biopsy for assessment of polyneuropathy. Nerve biopsy is generally accepted as useful in the evaluation of certain neuropathies as in patients with suspected amyloid neuropathy, mononeuropathy multiplex due to vasculitis, or with atypical forms of chronic inflammatory demyelinating polyneuropathy (CIDP). Skin biopsy is a validated technique for determining intraepidermal nerve fiber density and may be considered for the diagnosis of distal symmetric polyneuropathy (DSP), particularly small fiber sensory polyneuropathy (SFSN). The most common technique involves a 3 mm punch biopsy of the skin from the leg. After sectioning by microtome, the tissue is immunostained with anti-protein-gene product 9.5 (PGP 9.5) antibodies and examined with immunohistochemical or immunofluorescent methods [33]. Skin biopsy could be less invasive, validated, technically possible diagnostic tool for patients with GVHD who are at high risk to develop infection and/or bleeding.

cGVHD ANTIBODIES AND TREATMENT WITH RITUXIMAB

The investigation of the immune pathophysiology of chronic GVHD is limited and just a few animal models have been developed that mimic the various clinical manifestations of this disease in humans [34]. The effective prevention of chronic GVHD by the depletion of T cells from the stem cell graft demonstrates that donor T cells play a critical role in this disease. When patients and donors are HLA-matched, minor histocompatibility antigens expressed in normal tissues of the recipient have been shown to elicit both CD4+ and CD8+ T-cell responses which result in either direct cell killing or cytokine-induced tissue injury. Thus, current therapies for chronic GVHD are targeted primarily and non-specifically against donor T-cell activity. Although donor T cells play a central role in the development of chronic GVHD, there is emerging evidence that donor B cells also contribute to the clinical manifestations of this disease [35].

B cells

Twenty-four research groups have investigated the involvement of antibodies in the pathogenesis of cGVHD and found 35 different antibodies to be more prevalent in cGVHD [36]. Although not always analyzed, 8 autoantibodies and 5 alloantibodies seemed to be strongly associated with cGVHD (table 3).

Despite over 20 years of investigation, no studies have convincingly demonstrated that these antibodies contribute to the clinical manifestations of tissue injury in cGVHD. The location of most target antigens of these antibodies is intracellular and the antibodies do not have a direct cytolytic activity. In addition, tissue injury via immune complexes or vasculitis is not probable, as these are not prominent features of cGVHD.

Interesting data was published by Kim et all [37] who found higher levels of B cell activating factor (BAFF) in patients with active chronic GVHD at baseline than in normal controls [38]. Although not statistically significant, patients with lower pre-treatment BAFF levels tended to have better outcomes from therapy. Serum BAFF levels increased as B-cell numbers and immunoglobulin levels fell in response to rituximab therapy. This is consistent with the known function of BAFF as an important regulator of B-cell homeostasis and survival, and BAFF has previously been shown to play a critical role in B-cell reconstitution following myeloablative conditioning [38]. At normal basal levels, BAFF serves to promote survival of antigen-specific B cells; however, persistently high BAFF levels are also able to prevent apoptosis of auto-reactive B cells and promote the development of autoimmunity [39]. Earlier work from our laboratory showed that BAFF levels are higher in patients with chronic GVHD than in those without [40, 41]. Patients with chronic GVHD also have low numbers of B cells, and high BAFF/B cell ratios are, therefore, characteristic of active chronic GVHD. Patients who

Table 3. **Antibodies strongly associated with cGVHD**

Antibody	Author	Years of publication	Prevalence in cGVHD patients after HSCT
ANA	Lister et al. (Lister, 1987)	1987	38 % (n=26)
Anti-cytoskeletal intermediate filaments antibodies	Tazzari et al. (Tazzari, 1987)	1987	100 % (n=16)
Anti-cytoplasmic squamous epithelium antibodies	Lortan et al. (Lortan, 1992)	1992	42% (n=36)
Anti-nucleolar B23 antibodies	Wesierska-Gadek et al. (Wesierska-Gadek, 1992) Kier et al. (Kier, 1990)	1992; 1990	45 % (n=22)
Anti-nucleolar C23 antibodies	Wesierska-Gadek et al. (Wesierska-Gadek, 1992) Kier et al. (Kier, 1990)	1992; 1990	27 % (n=22)
Anti-H1 hytones antibodies	Wesierska-Gadek et al. (Wesierska-Gadek, 1992) Kier et al. (Kier, 1990)	1992; 1990	18% (n=22)
Anti-nuclear lamins	Wesierska-Gadek et al. (Wesierska-Gadek, 1992) Kier et al. (Kier, 1990)	1992; 1990	9% (n=22)
Anti-thyroid microsome antibodies	Lortan et al. (Lortan, 1992)	1992	43% (n=40)
Anti-PDGFR antibodies	Svegliati et al. (Svegliati, 2007)	2007	100% (n=22)
Anti-DBY antibodies	Miklos et al. (Miklos, 2004)	2004	50% (n=60)
	Miklos et al. (DB Miklos, 2005)	2005	47% (n=75)
Anti-UTY antibodies	Miklos et al. (DB Miklos, 2005)	2005	24% (n=75)
Anti-ZFY antibodies	Miklos et al. (DB Miklos, 2005)	2005	16% (n=75)
Anti-RPS4Y antibodies	Miklos et al. (DB Miklos, 2005)	2005	5% (n=75)
Anti-EIF1AY antibodies	Miklos et al. (DB Miklos, 2005)	2005	8% (n=75)

Adapted from Kapur, 2008.

do not develop chronic GVHD during the first year after hematopoietic stem cell transplantation have higher numbers of B cells at 6 and 9 months post-transplant than patients who do develop chronic GVHD. Further phenotypic analysis revealed that patients without chronic GVHD have higher proportions of nave CD27– B cells whereas patients who develop chronic GVHD have higher proportions of activated CD27+ B cells. These findings suggest that persistent elevation of BAFF in the setting of delayed B cell reconstitution can support the survival of activated, allo-reactive B cells and, therefore, promote the development of chronic GVHD. BAFF is also produced by myeloid cells in the setting of inflammation, and this may be another factor driving ongoing BAFF production once B-cell numbers recover in patients with chronic GVHD [42]. Interestingly, high doses of steroids have been shown to lower BAFF levels, and this may represent one of the mechanisms by which these agents lead to improvements in chronic GVHD.

A recent study indicated that recipient B cells are not important initiators of GVHD, and that efforts to prevent GVHD by antigen presenting cells (APC) depletion should focus on other APC subsets [43].

T cells

Recently, T-regulatory cells (Tregs) have been investigated. Tregs can suppress proliferation and function of T cells, particularly of the Th1 type. They are also known to constitutively express CD25+. In a murine model it was demonstrated that the incidence and severity of cGVHD is higher in the absence of recipient CD4+ CD25+ T cells, and the subsequent repletion with recipient or host Tregs resulted in a protective effect. *De novo* generation of donor CD4+ T cells during acute GVHD is of importance for the progression to cGVHD. CD52+ and anti-CD25+ antibodies have been shown to be effective in preventing cGVHD. However, these were small, phase I and II, single center studies. Therefore, a prospective controlled randomized multicenter study is highly warranted to confirm these promising results.

T and B cells collaboration

Several studies have suggested a possible collaboration between B and T cells in the pathogenesis of cGVHD. In addition, various studies demonstrated B-cell responses to certain antigens in cGVHD patients, indicating the collaboration of B and T cells to produce specific antibodies against host antigens. Moreover, Zorn et all demonstrated a coordinated B- and T-cell response in a male cGVHD patient after allogeneic HSCT with a female donor [44]. In this study, donor B cells were shown to mediate an alloimmune response and donor CD4+ T cells mediated an autoimmune response, via the development of anti-DBY antibodies. Furthermore, in cGVHD patients treated with rituximab, total lymphocytes decreased even more severely in number than B cells, suggesting that rituximab may somehow suppress T cells that interact with B cells.

MINOR HISTOCOMPATIBILITY ANTIGENS

Analysis of patients treated for post-transplantation relapse with donor lymphocytes has shown tumor regression to be correlated with expansion of cytotoxic T lymphocytes (CTLs) specific for hematopoiesis-restricted minor histocompatibility antigens (mHAs) [45, 46]. mHAs are peptides, presented by major histocompatibility complex (MHC) molecules, derived from intracellular proteins that differ between donor and recipient due mostly to single nucleotide polymorphisms (SNPs) or copy number variations (CNVs) [47–49]. Identification and characterization of mHAs that are specifically expressed in hematopoietic but not in other normal tissues could contribute to graft-versus-leukemia/lymphoma (GVL) effects, while minimizing unfavorable graft-versus-host disease, one of the most serious complications of allo-HSCT [47, 48].

A recent study, which analyzed the mHAs alloreactivity from 24 donor/recipient pairs and correlated such alloreactivity with the development of GVHD or absence of relapse, provided a robust method to monitor mH antigens graft-versus-host reaction and suggest that current identified mHAs have predictive value on GVHD and GVL [50].

Although donor T cells play the main role in the development of chronic GVHD, there is evidence that donor B cells also act in the clinical manifestations of this disease [51, 52]. It was demonstrated a correlation between cGHVD and development of antibody responses to H-Y minor histocompatibility antigens in cases of sex-mismatched (male recipients with female donors) allo-HCT. These findings provided the scientific rationale for a number of studies exploring rituximab, which acts for profound B-cell depletion, to treat patients with steroid-refractory cGVHD.

The retrospective studies identified small numbers of patients who responded to rituximab [53, 54]. These findings were confirmed by larger studies [55]. The meta-analysis of published rituximab studies in patients with steroid-resistant chronic GVHD revealed an overall response rate of 66%, with responses observed for disease involving the skin, oral mucosa, liver, and lung [56, 57]. Summarized several potential mechanisms through which donor B cells can contribute to the clinical manifestations of chronic GVHD. In most of these mechanisms, B cells do not act independently but modulate immune responses of other cells, primarily CD4+ and CD8+ T cells. For example, alloantibodies can form immune complexes with recipient minor histocompatability antigens and incorporation of these immune complexes by dendritic cells can stimulate donor T-cell responses specific for these minor histocompatability antigens. Extensive depletion of all mature B cells with rituximab should interrupt all of the pathways in which B cells interact with T cells and suppress both antibody-dependent and antibody-independent B-cell mechanisms associated with chronic GVHD. Providing effective therapy for chronic GVHD without compromising normal immune functions and the graft-*versus*-leukemia effect remain important challenges and well-designed and adequately powered prospective studies to conclusively address this issue are needed.

DIFFERENTIAL DIAGNOSIS

The best-described polyneuropathies in the setting of HSCT are those associated with chemotherapeutic drugs: etoposide, cisplatin, paclitaxel, cytarabine (Ara-C), cyclosporine, tacrolimus, and interferon-a [58]. Severity of neuropathy increases with duration of treatment and progression usually stops once drug treatment is completed. An exception are platinum compounds where sensory loss may progress for several months after discontinuation of treatment ("coasting"). Pre-existent neuropathy may influence the develpment of toxic neuropathy. The neurologist managing cancer patients who develop neu-

Table 4. **Peripheral neurotoxicity of chemotherapeutic agents**

Drug	Clinical features	Electrophysiological changes
Vinca alkaloids	Symmetric sensomotor polyneuropathy; autonomic neurophaty, rarely cranial neuropathies	Axonal sensorimotor polyneuropathy; denervation in distal muscles
Cisplatin	Predominant sensory neuropathy; sensory ataxia; Lhermitte's sign	Low-amplitude or unobtainable SNAPs; motor NCS and EMG usually normal
Oxaliplatin	Predominant sensory neuropathy; sensory ataxia; Lhermitte's sign	Low-amplitude or unobtainable SNAPs; EMG with neuromyotonic discharges in acute cases
Taxanes	Symmetric predominantly sensory polyneuropathy; rare autonomic symptoms	Axonal sensorimotor polyneuropathy; denervation in distal muscles
Thalidomide	Symmetric sensorimotor polyneuropathy; autonomic neuropathy; sensory ataxia and spasticity in severe cases	Axonal sensorimotor polyneuropathy; denervation in distal muscles
Bortezomib	Often, mild to moderate distal sensory loss, suppression of deep tendon reflexes, proprioception abnormalities. Mild to very severe pain, mainly at fingertips and toes. Usually, mild motor weakness in distal muscles of the lower limbs.	**NCS:** Reduction of a-SNAPs and CMAPs. Mild distal slowing of sensory and motor conduction velocities and increase in distal motor latencies. **EMG:** Active denervation changes with fibrillation potentials and increased size and complexity of motor unit potentials from distal muscles of the lower limbs.

SNAPs – sensory nerve action potentials; NCS – nerve conduction study; EMG – electromyography; CFS – cerebrospinal fluid

Differential diagnosis and treatment algorithm of myopathy after HSCT
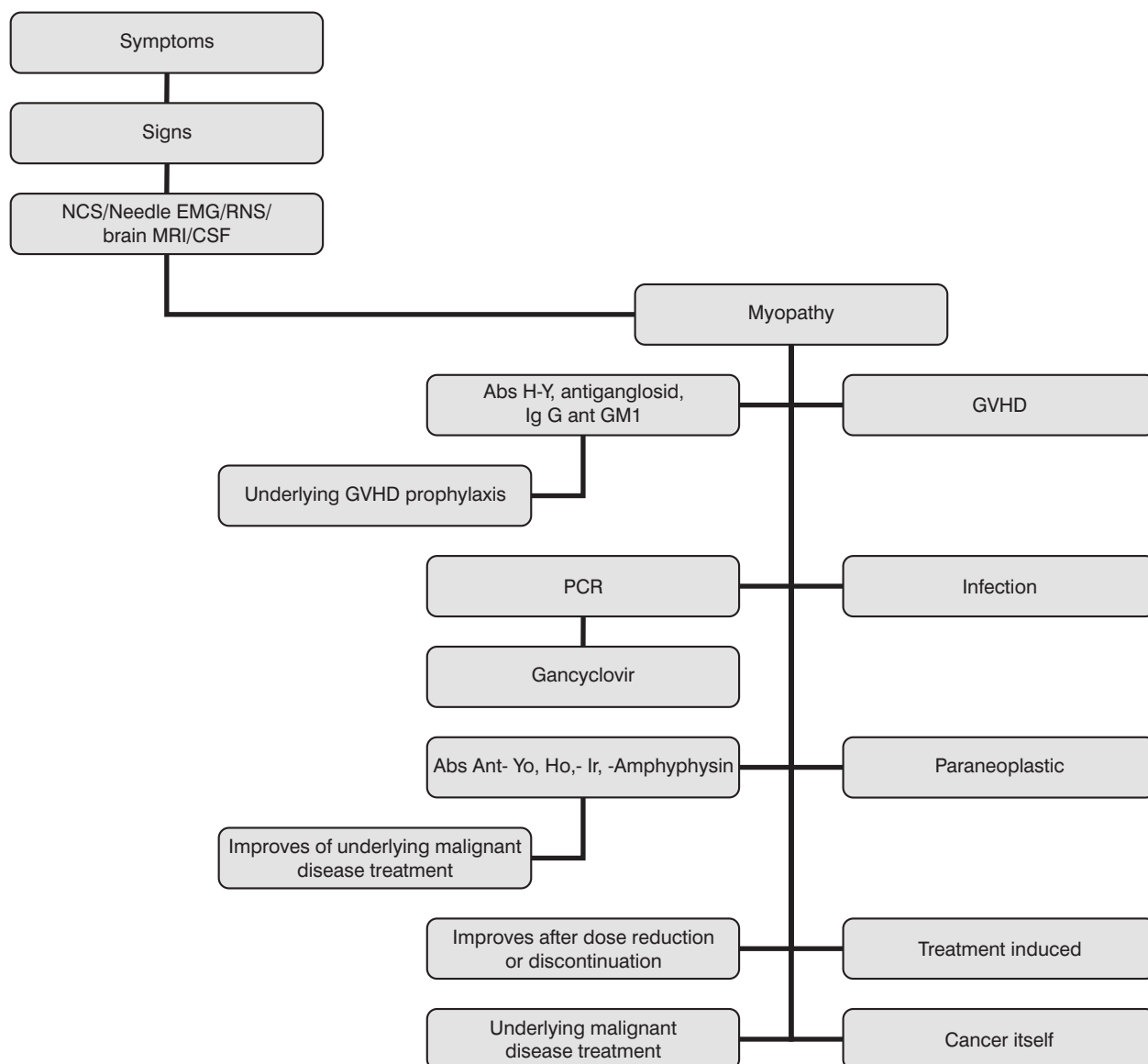

Fig. 1. **NCS** – nerve conduction studies, **RNS** – repetitive nerve stimulation, **EMG** – electromyography, **MRI** – magnetic resonance imaging, **CSF** – cerebrospinal fluid, **Abs** – antibodies.
Supportive treatment: Plasma exchange, Steroids, Intravenous Immunoglobulin, Monoclonal antibody against CD20, symptomatic treatment.

ropathy must answer a series of important questions as follows: 1) Are the symptoms due to peripheral neuropathy or myopathy? 2) Is the neuropathy due to to the underlying disease or the treatment? 3) Should treatment be modified or stopped because of neuropathy? 4) What is the best supportive care in terms of pain management or physical therapy for each patients [59]?

Other iatrogenic factor is radiation which can induce plexopathies after doses greater than 6000 rads and this peripheral nervous system damage presents from 3 months to 26 years (mean of 6 years) after treatment [60]. Radiation – induced *Cauda equina* syndrome occurs from 3 months to 25 years caused by total dose of greater than 4000 cGy [61].

Another differential diagnosis is steroid myopathy which is evidently important, because polymyositis requires starting or increasing prednisone as opposed to discontinuation in the case of steroid myopathy. Elecromyography (EMG) and occasionally muscle biopsy are very important tool for correct diagnosis [62].

Neurologic paraneoplastic syndromes are disorders associated with cancer but are not caused by local effects of the primary tumor mass. Instead, they are considered to be "remote effects" of cancer that result in autoimmunity—antibodies or inflammatory cells that are directed against neural antigens expressed by the tumor [63]. These syndromes can appear before any symptoms related to the cancer itself developed; sometimes, they may precede can-

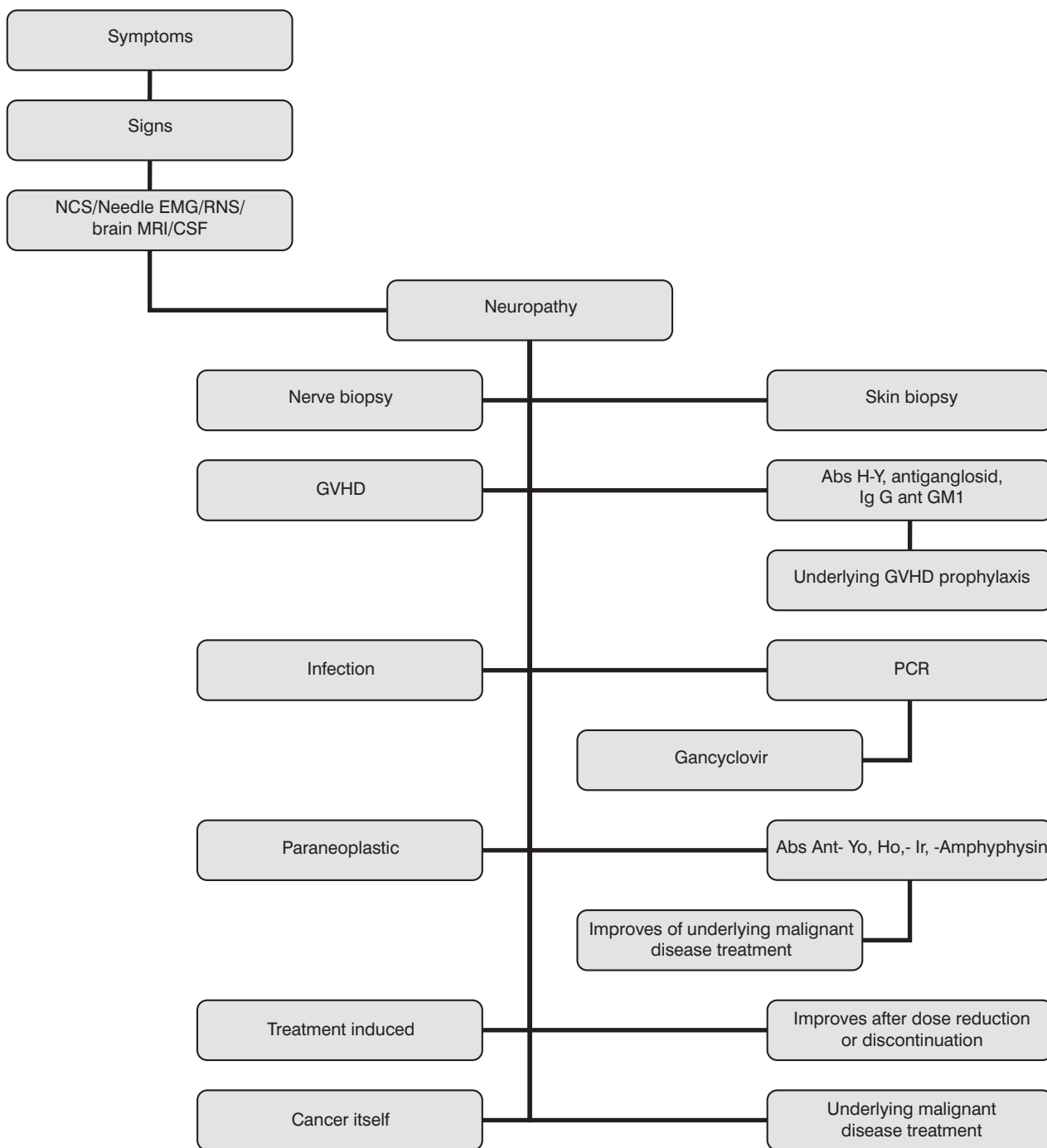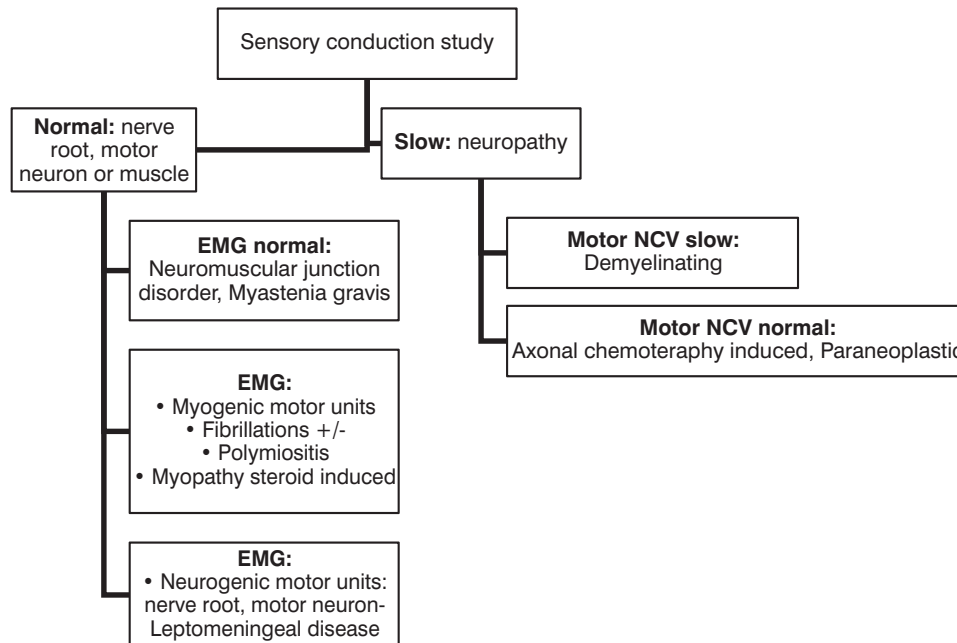## Differential diagnosis and treatment algorithm of neuropathy after HSCT

Symptoms

Signs

NCS/Needle EMG/RNS/ brain MRI/CSF

Neuropathy

Nerve biopsy — Skin biopsy

GVHD — Abs H-Y, antiganglosid, Ig G ant GM1

Underlying GVHD prophylaxis

Infection — PCR

Gancyclovir

Paraneoplastic — Abs Ant- Yo, Ho,- Ir, -Amphyphysin

Improves of underlying malignant disease treatment

Treatment induced — Improves after dose reduction or discontinuation

Cancer itself — Underlying malignant disease treatment

Fig. 2. **NCS** – nerve conduction studies, **RNS** – repetitive nerve stimulation, **EMG** – electromyography, **MRI** – magnetic resonance imaging, **CSF** – cerebrospinal fluid, **Abs** – antibodies.
Supportive treatment: Plasma exchange, Steroids, Intravenous Immunoglobulin, Monoclonal antibody against CD20, symptomatic treatment.

cer diagnosis 2 years or more [64]. Paraneoplastic sensory neuronopathy most frequently is associated with the presence of anti-Hu antibodies, which also are known as antineuronal nuclear antibody type 1 (ANNA-1). Symptoms progress sub-acutely to involve the limbs, trunk, and face, causing severe sensory ataxia and pseudoathetosis. The CSF may show mild lymphocytic pleocytosis (20–40 lymphocytes/mm^3), and moderate protein elevation [65]. Oligoclonal bands may be present [66]. The malignancy most commonly associated with sensory neuronopathy is small cell lung cancer (SCLC). Other malignancies encountered less frequently include cancers of the breasts, ovaries, prostate, adrenal gland, as well as neuroblastoma and Hodgkin's lymphoma [66]. Discovery

A. Straukienė, K. Andrėkutė, V. Pečeliūnas, R. Meškauskas, J. Wanschitz, W. Löscher, V. Budrys

Evaluation of lower motor neuron weakness
in hematopoietic stem-cell transplantation patients

(Data from Openshaw H, Slatkin NE. Differential diagnosis of neurological complications
in bone marrow transplantation. The Neurologist 1995; 1: 191–206.)

Fig. 3. **NCV** – nerve conduction velocity, **EMG** – electromyography.

and treatment of the underlying cancer occasionally lead to improvement in the neurologic symptoms.

Peripheral neuropathy and myopathy are frequently associated with infections, particularly with HZV, EBV, CMV after HSCT [8, 67]. 13 from 19 with Guillain–Barre' syndrome (GBS) had antecedent infections which significantly correlated with the disease p<0,0008 [68].

Vasculitic neuropathy (VN) can be a part of systemic vasculitis which occurs in 60–70% of patients. It also can be as a nonsystemic vasculitic neuropathy. VN presents either typically as mononeuritis multiplex, an asymmetric sensorimotor neuropathy or, less frequently, as a distal symmetric neuropathy ("small vessels vasculopathy") [69]. Neuropathies are painful in more than 80% of patients. Histological studies show multiple focal lesions, with T and B cells involvement.

Openshaw et all suggest the allgorithm to evaluate the lower motor neuron weakness in patients after HSCT [70] (Fig. 3).

We believe that immunologically mediated neuropathies may occur after autologous and allogeneic HSCT, and frequently lead to severe motor more than sensory symptoms and signs. Acute Guillain-Barre syndromes (GBS) and more protracted chronic forms (chronic inflammatory demyelinating polyneuropathies) (CIDP), myasthenia gravis (MG) or polymyositis (PM), have been de-

scribed, almost all as case reports. The evidence for immune-associated mechanisms was circumstantial, based on the presence of multisystemic organ GVHD, response to plasmapheresis or corticosteroids [71].

To summarize all analyzed publications we recommend the algorithms for diagnostic and treatment purpose (Fig. 1, 2).

CONCLUSION

Establishing whether histopathological findings dominate in peripheral neuropathies or myopathies would help to evaluate proper treatment. Reduction or increasing drug doses may precede the onset, thus supporting the immune-mediated or steroid induced hypothesis.

Better outcomes of neurological complications would improve quality of life and decrease morbidity and mortality after HSCT. Prospective studies in this area focussing on complex clinical neurological syndromes, neuropathology, neurophysiologic tests and neuroradiologic imaging studies in large transplantation centers using clinical registries and strategies are strongly needed.

References

1. Flowers MED, Kansu E. Late complications of hematopoietic stem cell transplantation. Medicina, Ribeirćo Preto, Simpósio: Transplante de medulla ossea – 2 parte. 2000; 33: 415–32.

2. Martin PJ, Couriel D, Flowers ME, et al. A survey of diagnosis, management and grading of Chronic GVHD. Biol Blood Marrow Transplant 2002; 8: 32–9.

3. Storb R, Goerner M, Gooley T, et al. Morbidity and mortality of chronic GVHD after hematopoietic stem cell transplantation from HLA-identical siblings for patients with aplastic or refractory anemias. Biol Blood Marrow Transplant 2002; 8: 47–56.

4. Thomas ED, Shulman HM, Sullivan KM, et al. Chronic graft-versus-host syndrome in man. A long-term clinico-pathologic study of 20 Seattle patients. Am J Med 1980; 69: 204–17.

5. Snover DC. Acute and chronic graft versus host disease: histopathological evidence for two distinct pathogenetic mechanisms. Hum Pathol 1984; 15: 202–5.

6. Santos GW, Beschorner WE, Patchell RA, et al. Neurologic complications of bone marrow transplantation. Neurology 1985; 35: 300–6.

7. Rozman C, Tolosa E, Carreras E, et al. Neurologic complications of autologous and allogeneic bone marrow transplantation in patients with leukemia: a comparative study. Neurology 1996; 46: 1004–9.

8. Pa B, Charles ED, August S, Packer RJ, Wiznitzer M. Neurological complications of bone marrow transplantation in childhood. Ann Neurol 1984; 16: 569–76.

9. Vinters HV, Mohrmann RL, Mah V. Neuropathologic findings after bone marrow transplantation: an autopsy study. Hum Pathol 1990; 21: 630–9.

10. Grañena A, Gallardo D, Ferrà C, et al. Neurologic complications after allogeneic bone marrow transplantation. Bone Marrow Transplant 1996; 18: 1135–9.

11. van den Bent MJ, de Brabander C, Cornelissen J, et al. Increased incidence of neurological complications in patients receiving an allogenic bone marrow transplantation from alternative donors. J Neurol Neurosurg Psychiatry 2000; 68: 36–40.

12. Straube A, et al. Prospective evaluation of neurological complications after allogeneic bone marrow transplantation. Neurology 2003; 60: 842–8.

13. de Medeiros CR, Pasquini R, Loddo G, et al. Neuropathological findings after bone marrow transplantation: an autopsy study of 180 cases. Bone Marrow Transplant 2000; 25: 301–7.

14. Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of clinical oncology 2008, Clinical practice guideline update: Use of chemotherapy and radiation therapy protectants. Journal of Clinical Oncology 2009; 27(1): 127–45.

15. Nagashima K, Nagashima T, Sato F, et al. Chronic demyelinating polyneuropathy in graft-versus-host disease following allogeneic bone marrow transplantation. Neuropathology 2002; 22: 1–8.

16. Bierman P, Bashir R, Snider S. Neurologic complications after high-dose chemotherapy and autologousbone marrow transplantation for Hodgkin's disease. Neurology 1994; 44: 681.

17. Straube A, Kolb H-J, Holler E, et al. Neurological and neuroradiological findings in long-term survivors of allogeneic bone marrow transplantation. Annals of Neurology 1998; 43: 627–33.

18. Werneck LC, Lorenzoni PJ, Scola RH, et al. Chronic inflammatory demyelinating polyradiculoneuropathy in chronic graft-versus-host disease following allogeneic hematopoietic stem cell transplantation. Arq Neuropsiquiatr 2007; 65(3-A): 700–4.

19. Mendell JR, Amato AA, Barohn RJ, et al. Polyneuropathy complicating bone marrow and solid organ transplantation. Neurology 1993; 43: 1513–8.

20. Krance RA, Rodriguez V, Kuehnle I, et al. Guillain–Barre syndrome after allogeneic hematopoietic stem cell transplantation Bone Marrow Transplantant. Bone Marrow Transplantation 2002; 29: 515–7.

21. Antin JH, Soiffer RJ, Herbst RS, et al. Guillain–Barre syndrome following allogeneic bone marrow transplantation. Neurology 1997; 49: 1711–4.

22. Hahn AF. Guillain–Barre syndrome. Lancet 1998; 352: 635–41.

23. Rostami A, Sater RA. Treatment of Guillain-Barre syndrome with intravenous immunoglobulin. Neurology 1998; 51(Suppl. 5): S9–15.

24. Storb R, Thomas ED, Nims J, et al. Myasthenia gravis after allogeneic bone marrow transplantation: relationship to chronic graft-versus-host disease. Neurology 1986; 36: 1087–91.

25. Urbano Marquez A, Rozman C, Granena A, et al. Myasthenia gravis after allogeneic bone marrow transplantation case and pathogenetic considerations. Bone Marrow Transplant 1990; 5: 435–7.

26. Sladky JT, Maguire H, August CS, Adams C. Neuromuscular complications of bone marrow transplantation. Pediatric Neurology 1995; 12: 58–61.

27. Harada M, Abe K, Yoshino T, et al. Myositis as a manifestation of chronic graft-versus-host disease. Intern Med 2000; 39: 482–5.

28. White AC, Leano AM, Miller K. Chronic graft-versus-host disease–related polymyositis as a cause of respiratory failure following allogeneic bone marrow transplant. Bone Marrow Transplant 2000; 26: 1117–20.

29. Brain MC, Leber B, Walker IR, et al. Reinduction of remission of chronic myeloid leukemia by donor leukocyte transfusion following relapse after bone marrow transplantation: recovery complicated by initial pancytopenia and late dermatomyositis. Bone Marrow Transplantant 1993; 12(4): 405–7.

30. Nelson JL, Sullivan KM, Stevens AM. Polymyositis as a manifestation of chronic graft-versus-host disease. Rheumatology 2002; 42: 34–9.

31. Werneck LC, Pasquini R, Teive HAG, et al. Chronic inflammatory demyelinating polyradiculoneuropathy in chronic graft-versus-host disease following allogeneic hematopoietic stem cell transplantation: case report. Arquivos de Neuro-Psiquiatria 2007; 65(3a).

32. Rozman C, Palou J, Martin-Ortega E, et al. Inflammatory myopathy associated with chronic graft-versus-host disease. Neurology 1986; 36: 1091–3.

33. Sumner AJ, England JD, Gronseth GS, et al. Practice parameter: the evaluation of distal symmetric polyneuropathy: the role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). American Academy of Neurology 2009; 1(1): 14–22.

34. Gress RE, Chu YW. Murine models of chronic graft-versus-host disease: insights and unresolved issues. Biol Blood Marrow Transplant 2008; 14(4): 365–78.

35. Bergwelt-Baildon MS, Shimabukuro-Vornhagen A, Hallek MJ, Storb RF. The role of B cells in the pathogenesis of graft-versus-host disease. Blood 2009; 114(24): 4919–27.

36. Hagenbeek A, Kapur R, Ebeling S. B-cell involvement in chronic graft-versus-host disease. Haematologica 2008; 93(11): 1702.

37. Won JH, Kim SJ, Lee JW, et al. Weekly rituximab followed by monthly rituximab treatment for steroid-refractory chronic graft-versus-host disease: results from a prospective multicenter phase II study. Haematologica 2010; 95(11): 1935–42.

38. Kanhai HH, van den Akker ES, Oepkes D, et al. Noninvasive antenatal management of fetal and neonatal alloimmune thrombocytopenia: safe and effective. BJOG 2007; 114(4): 469–73.

39. Macfarland JG, Bussel JB, Berkowitz RL, et al. Intracranial hemorrhage in alloimmune thrombocytopenia: stratified management to prevent recurrence in the subsequent affected fetus. Am J Obstet Gynecol 2010; 203(2): 135.e1–14.

40. Waters AH, Kaplan C, Murphy MF, Kroll H. Feto-maternal alloimmune thrombocytopenia: antenatal therapy with IvIgG and steroids–more questions than answers. European Working Group on FMAIT. Br J Haematol 1998; 100(1): 62–5.

41. Kekomäki R, Sainio S, Teramo K. Prenatal treatment of severe fetomaternal alloimmune thrombocytopenia. Transfus Med 1999; 9(4): 321–30.

42. Tutschek B, Giers G, Wenzel F, et al. Fetal alloimmune thrombocytopenia and maternal intravenous immunoglobin infusions. Haematologica 2010; 95(11): 1921–6.

43. Shlomchik WD, Matte-Martone C, Wang X, et al. Recipient B cells are not required for graft-versus-host disease induction. Biology of Blood and Marrow Transplantation 2010; 16: 1222–30.

44. Zorn E, Miklos DB, Floyd BH, et al. Minor histocompatibility antigen DBY elicits a coordinated B and T cell response after allogeneic stem cell transplantation. The Journal of Experimental Medicine 2004; 199: 1133–42.

45. Dolstra H, de Rijke B, van Horssen-Zoetbrood A, et al. A frameshift polymorphism in P2X5 elicits an allogeneic cytotoxic T lymphocyte response associated with remission of chronic myeloid leukemia. J Clin Invest 2005; 115: 3506–16.

46. Falkenburg JH, Marijt WA, Heemskerk MH, et al. Hematopoiesis-restricted minor histocompatibility antigens HA-1- or HA-2-specific T cells can induce complete remissions of relapsed leukemia. Proc Natl Acad Sci USA, 2003; 100(5): 2742–7.

47. Riddell SR, Bleakley M. Molecules and mechanisms of the graft-versus-leukaemia effect. Nat Rev Cancer 2004; 4: 371–80.

48. Goulmy E, Spierings E. Expanding the immunotherapeutic potential of minor histocompatibility antigens. J Clin Invest 2005; 115: 3397–400.

49. Goulmy E, Oguz F, Oudshoorn M, et al. Phenotype frequencies of autosomal minor histocompatibility antigens display significant differences among populations. PLoS Genet 2007; 3: e103.

50. Garban F, Laurin D, Hannani D, et al. Immunomonitoring of graft-versus-host minor histocompatibility antigen correlates with graft-versus-host disease and absence of relapse after graft. Transfusion 2010; 50: 418–28.

51. Shimabukuro-Vornhagen. The role of B cells in the pathogenesis of graft-versus-host disease. Blood 2009; 114(24): 4919–27.

52. Miklos, DB. Antibody response to DBY minor histocompatibility antigen is induced after allogeneic stem cell transplantation and in healthy female donors. Blood 2004; 103: 353–9.

53. Ratanatharathorn V. Treatment of chronic graft-versus-host disease with anti-CD20 chimeric monoclonal antibody. Biol Blood Marrow Transplant 2003; 9: 505–11.

54. Dijk C. Anti-CD20 monoclonal antibody treatment in 6 patients with therapy-refractory chronic graft-versus host disease. Blood 2004; 104(8): 2603–6.

55. Zaja F. Treatment of refractory chronic GVHD with rituximab: a GITMO study. Bone Marrow Transplantation 2007; 40: 273–7.

56. Kharfan-Dabaja. Rituximab is feasible to administer to allograft recipients with advanced CD20+ malignancies and does not affect timely hematopoietic engraftment. Biol Blood Marrow Transplant 2008; 14: 121–2.

57. Ritz J, Jacobson CA. B-cell-directed therapy for chronic graft-versus-host disease. Haematologica 2010; 95: 1811–3.

58. Burns TM, Falah M, Schiff D. Neuromuscular complications of cancer diagnosis and treatment. J Support Oncol 2005; 3: 271–82.

59. Grisold AJ, Windebank W. Chemotherapy-induced neuropathy. Journal of the Peripheral Nervous system 2008; 13: 27–46.

60. Posner JB, Kori SH, Foley KM. Brachial plexus lesions in patients with cancer: 100 cases. Neurology 1981; 31: 45–50.

61. Donaghy M, Bowen J, Gregory R, Squier M. Post-irradiation lower motor neuron syndrome: neuronopathy or radiculopathy. Brain 1997; 119: 1429–39.

62. Forman SJ, Parker PM, Openshaw H. Myositis associated with graft-versus-host disease. Curr Opin Rheumatol 1997; 9: 513–9.

63. Voltz R, Graus F, Delattre JY, et al. Recommended diagnostic criteria for paraneoplastic syndromes. J Neurol Neurosurg Psychiatry 2004; 75: 1135–40.

64. Posner JB, Anderson NE, Cunningham JM. Autoimmune pathogenesis of paraneoplastic neurological syndromes. Crit Rev Neurobiol 1987; 3: 245–99.

65. Lennon VA. The case for a descriptive generic nomenclature: clarification of immunostaining criteria for PCA-1, ANNA-1, and ANNA-2 autoantibodies. Neurology 1994; 44: 2412–5.

66. Lennon VA, Pittock SJ, Kryzer TJ. Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. Ann Neurol 2004; 56: 715–9.

67. Patchell RA, Davis DG. Neurologic complications of bone marrow transplantation. Neurol Clin 1988; 6: 377–87.

68. Okamoto S, Suzuki S, Mori T, et al. Immune-mediated motor polyneuropathy after hematopoietic stem cell. Bone Marrow Transplantation 2007; 40(3): 289–91.

69. Lagueny A, Vital C, Vital A, et al. Combined nerve and muscle biopsy in the diagnosis of vasculitic neuropathy. A 16-year retrospective study of 202 cases. Muscle Nerve 1999; 11(1): 20–9.

70. Openshaw H. Exacerbation of inflammatory demyelinating polyneuropathy after bone marrow transplantation. Bone Marrow Transplant 1991; 7: 411–4.

71. Wijdicks Eelco FM, Krouwer Hendrikus GJ. Neurologic complications of bone marrow transplantation. Neurol Clin N Am 2003; 21: 319–52.

A. Straukienė, K. Andrėkutė, V. Pečeliūnas,
R. Meškauskas, J. Wanschitz, W. Löscher, V. Budrys

NEUROPATIJOS IR MIOPATIJOS
ONKOHEMATOLOGINIŲ LIGŲ ATVEJU PO
KAMIENINIŲ KRAUJO LĄSTELIŲ
TRANSPLANTACIJOS, KAI PASIREIŠKIA
TRANSPLANTANTO PRIEŠ ŠEIMININKĄ LIGA:
LITERATŪROS APŽVALGA

Santrauka

VULSK hematologijos, onkologijos, transfuzologijos centre kasmet atliekama apie 100–120 kamieninių kraujodaros ląstelių transplantacijų. Pagal transplantuojamų ligonių skaičių šis centras prilygsta Universitetinės Insbruko ligoninės hematologijos ir kaulų čiulpų transplantacijos centrui Austrijoje. Kamieninių kraujodaros ląstelių transplantacija (KKLT) – tai gydymo metodas, kai, skiriant potencialiai neurotoksinius vaistus, supresuojama imuninė sistema ir sunaikinamos navikinės ląstelės. KKLT gydomos onkohematologinės ligos, aplastinė anemija ir metaboliniai sutrikimai.

Šių dienų aktuali potransplantacinė problema – neurologinės komplikacijos, pasitaikančios nuo 37 iki 91 %, sudaranti nuo 6 iki 26 % pagrindinių mirties priežasčių. Bendrą pacientų būklę sunkinanti aplinkybė – autoimuninės sistemos suaktyvėjimas prieš transplantantą, vadinama transplantanto prieš šeimininką liga (TPŠL). Kai ši imuninės sistemos aktyvacija pasireiškia po transplantacijos praėjus 100 d., ji vadinama lėtine TPŠL. Dažniausi lėtinės TPŠL pažeidžiami organai taikiniai yra virškinimo trakto organai, kepenys, oda, plaučiai. Kol kas nėra daug duomenų apie nervų sistemos pažeidimą, esant TPŠL.

Šiame straipsnyje pagrindinis dėmesys skiriamas periferinės nervų sistemos pažeidimams (lėtinė uždegiminė demielinizuojanti poliradikuloneuripatija, Guillain-Barre sindromas), nervoraumens jungties ligoms (miastenija) ir miopatijų pasireiškimui po kamieninių kraujodaros ląstelių transplantacijos, esant TPŠL. Dėl nuolatinės imunosupresijos bei chemopreparatų neurotoksinio poveikio TPŠL, kai pažeidžiama periferinė nervų sistema, klinika yra maskuota, o diagnostika sudėtinga. Straipsnyje aprašomos refrakterinių gliukokortikoidams TPŠL formų gydymo rekomendacijos rituksimabu bei odos biopsijos histologinio tyrimo alternatyvos. pateikiamos apibendrintos diagnostikos ir gydymo rekomendacijos visoms tikėtinoms periferinės nervų sistemos pažeidimo ir raumens ligoms, esant TPŠL, nustatyti.

Raktažodžiai: kamieninių kraujodaros ląstelių transplantacija, imunosupresija, transplantanto prieš šeimininką liga, Guillain-Barre sindromas, miastenija, rituksimabas.