REVIEW

Autologous haematopoietic stem cell transplantation for neurological diseases

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ABSTRACT
Neuroinflammatory diseases such as multiple sclerosis, neuromyelitis optica, chronic inflammatory demyelinating polyneuropathy and myasthenia gravis are leading causes of physical disability in people of working age. In the last decades significant therapeutic advances have been made that can ameliorate the disease course. Nevertheless, many affected will continue to deteriorate despite treatment, and the costs associated with disease-modifying drugs constitute a significant fiscal burden on healthcare in developed countries. Autologous haematopoietic stem cell transplantation is a treatment approach that aims to ameliorate and to terminate disease activity. The erroneous immune system is eradicated using cytotoxic drugs, and with the aid of haematopoietic stem cells a new immune system is rebuilt. As of today, more than 1000 patients with multiple sclerosis have been treated with this procedure. Available data suggest that autologous haematopoietic stem cell transplantation is superior to conventional treatment in terms of efficacy with an acceptable safety profile. A smaller number of patients with other neuroinflammatory conditions have been treated with promising results. Herein, current data on clinical effect and safety of autologous haematopoietic stem cell transplantation for neurological disease are reviewed.

INTRODUCTION

Haematopoietic stem cell transplantation (HSCT) has been in use for treatment of malignancies since the 1950s.[1 2] In the last two decades it has been used for treatment of autoimmune diseases of the nervous system such as multiple sclerosis (MS), neuromyelitis optica (NMO), chronic idiopathic demyelinating polyneuropathy (CIDP) and myasthenia gravis (MG). Treatment with HSCT operates on the basic assumption that the origin of neuroinflammatory disease lies with the immune system and is dependent on immunological memory. In difference to currently available therapies, treatment with HSCT aims to erase the erroneous immune system and enable the formation of a new and self-tolerant immune system. As a consequence, most patients will not require additional therapy after the procedure.

Basic concepts
HSCT can be performed with stem cells collected from another individual (allogeneic transplantation) or from the same patient who will receive them (autologous transplantation). Autologous HSCT is preferred for treatment of autoimmune disease,

since allogeneic HSCT is associated with high treatment-related mortality (TRM), mainly due to graft versus host reactions. The procedure can be divided into four parts: the mobilisation, when drugs such as granulocyte colony-stimulating factor are administrated to mobilise haematopoietic stem cells (HSCs) from the bone marrow; the harvest, when stem cells are acquired through leukapheresis; the conditioning, when drugs, biologics and/ or radiation are given to 'ablate' the pathological immune system; and finally the reinfusion of autologous HSCs. To ensure that surviving lymphocytes present in the graft are eliminated, ex vivo or in vivo lymphocytic purging with antithymocyte globulin (ATG) is performed. Today, radiation and ex vivo purging are rarely used.

One common misconception is that the HSCs are the therapeutic product. HSCs do not differentiate into neurons or oligodendrocytes, and there is no evidence that they can repair damaged central nervous system (CNS) tissue. In vivo, HSCs differentiate in a haematopoietic lineage-restricted manner to erythrocytes, thrombocytes and lymphocytes, and shorten the interval of conditioning regimen-induced cytopaenias. The term 'autologous hematopoietic stem cell transplantation' is somewhat misleading in this regard, since the autologous stem cells are a supportive blood product that speeds recovery, rather than the focus of this therapy, and instead many favour the somewhat cumbersome terminology 'high-dose immunosuppressive therapy with hematopoietic stem cell support'.

Another important distinction is that HSCT should be viewed as a treatment principle rather than a single treatment. Various conditioning regimens have been used to reach the goal of immunoablation, which must be kept in mind when studies are compared. One commonly used classification of conditioning regimens is a subdivision into high-intensity regimens, including busulfan or total body irradiation (TBI); low-intensity regimens containing cyclophosphamide and ATG; and intermediate regimens such as BEAM, which is the combination of carmustine (BCNU), etoposide, cytarabine (Ara-C) and melphalan.[3]

The adverse events of the procedure can be divided into acute toxicity and long-term side effects. Acute toxicity gives rise to the well-known and expected side effects of alopecia, anaemia, thrombocytopaenia and leucopenia. Many patients also experience fever with or without bacteraemia. Such adverse events are effectively managed with supportive blood products and antibiotics. Acute

toxicity is directly related to the intensity of the conditioning regimen, with significantly more toxicity and TRM in high-intensity conditioning regimens. Long-term side effects have been less studied, and this is a serious gap in the knowledge base of this treatment. The main concerns are viral reactivations, development of secondary autoimmunity, malignancies and impaired fertility.

A HISTORICAL PERSPECTIVE

For a long time it was believed that the underlying defect of autoimmune diseases resided in the HSC. Early on, it was noted that haematopoietic radiation chimaeras between rodent strains that were susceptible or resistant to autoimmune disease sometimes developed disease and sometimes not, and that this propensity was generally dictated by the genotype of the bone marrow.[4] Thus it made little sense to use autologous HSCT in the treatment of such diseases. This notion was challenged in the early 1990s, when it was demonstrated that rats with adjuvant arthritis responded just as well to autologous or syngeneic bone marrow transplantation as to grafting with allogeneic bone marrow.[5] Soon thereafter, several groups reported on the effects of autologous or syngeneic HSCT for experimental autoimmune encephalomyelitis (EAE).[6–10] These studies showed that immunoablation by TBI or high-dose cyclophosphamide followed by HSCT could prevent the development of paralysis in SJL mice or Lewis rats. Post-transplant animals were resistant to reinduction of disease, and histological evidence of inflammation within the CNS was absent.

These early animal studies unmasked limitations of autologous HSCT because the results of autologous HSCT in SJL mice are dependent on disease stage. Animals treated early after disease induction had enduring improvement in disability, while there was no neurological improvement in animals treated in the chronic phase of EAE.[11] EAE is an autoimmune demyelinating disease induced by vaccination with myelin epitopes, but if demyelination is due to a persistent CNS viral infection as is the case in Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV), HSCT results in further neurological deterioration from viral hyperinfection of the CNS.[12] In clinical practice, neuroinflammatory disease responds to HSCT similar to the autoimmune EAE model and not the virally induced TMEV model.

Based on experiences from such animal studies, Burt et al[13] suggested that autologous HSCT should be tried for aggressive inflammatory MS. However, when Fassas et al[14] performed the first autologous HSCT for MS in April 1995, it was limited to secondary progressive MS for safety reasons. Their experiences with 15 patients were summarised in a seminal paper published in 1997, which set the stage for the coming years. The treatment could 'be used with relative safety', and some evidence was found that 'this kind of therapy can suppress disease progression and reduce disability'.[14] In the following years many groups reported outcome from treatment of mainly secondary progressive MS (SPMS) or primary progressive MS (PPMS) patients in small case series.[15–23] With increasing experience from more centres, the results were disappointing and many patients continued to deteriorate, especially with longer follow-up.[24 25] This was forthrightly summarised by Burt et al,[18] who reported that HSCT in secondary progressive MS with high expanded disability status scores (EDSS >6.0) was a failure and ineffective in preventing disease progression. At this point very few patients with RRMS were treated, but it was noted that patients with RRMS improved in the EDSS score[18] and that the effect on the

development of new MRI lesions was profound. In one study, the number of gadolinium-enhancing lesions was decreased from 656 in 18 patients pretherapy, to 7 post-HSCT.[26] The turning point came in 2009, when two independent groups reported that HSCT could completely abrogate disease activity in a majority of RRMS patients.[27 28] These and similar reports led to the 2012 consensus recommendations that HSCT should be considered as a therapeutic option at second line or beyond for patients with RRMS who deteriorate despite standard therapy.[29] As a first, HSCT was approved for treatment of RRMS on the national level by the Swedish Board of Health and Welfare in 2016.[30]

A large majority of published reports on HSCT for neurological conditions have been made on MS, reflecting the higher prevalence. Prompted by the good treatment responses in MS, HSCT was eventually tried for other neuroinflammatory diseases as well. In CIDP and MG, some case reports of successful outcome were published about 10 years ago; the first report of HSCT for CIDP appeared in 2002[31] and for MG in 2005.[32] Recently a register-based study from the European Society for Blood and Marrow Transplantation (EBMT) was published, reporting outcome of patients with NMO treated with HSCT.[33]

MULTIPLE SCLEROSIS

Several reports with data from the EBMT registry have been published on HSCT for MS, which highlight some of the difficulties encountered in registry-based studies[3 34 35] Validity of data can be put into question since registry data are not vetted by site visits for accuracy of disease stage, experience and certification of physician doing disease scoring. In addition, this group of patients is heterogeneous and has been treated with different regimens and different standard of care guidelines. Finally, the registry includes patients from centres with variable experience with the procedure, where some centres have performed only a handful of transplants, which has been identified as a risk factor for TRM.[3] Such elements will confound data interpretation significantly.

In addition to the reports of registry data, a large number of uncontrolled studies have been published over the years. In the initial studies, clarifying outcome and toxicity between trials is complicated due to heterogeneity in disease stage (RRMS, SPMS, PPMS), entry criteria (whether by disease progression or number of relapses), conditioning regimens and treatment guidelines. A summary of these trials was recently tabulated.[36] By now, it is established that HSCT has a profound effect on inflammation in MS and that it prevents relapses, new MRI lesions and disability in RRMS to a high degree. Whether HSCT also has a beneficial effect in SPMS or PPMS is at present unknown, and as a consequence we will summarise only the trials concerning chiefly RRMS.

We identified four studies containing at least 10 RRMS patients describing the outcome of a total of 188 RRMS patients (table 1).[37–40] Further, we will discuss the recently published The Autologous Haematopoietic Stem Cell Transplantation trial in MS (ASTIMS) study, which at present is the only reported randomised controlled trial.[41]

Efficacy

Only one randomised controlled trial of HSCT for MS has been reported in the literature: the ASTIMS trial,[41] which was prematurely terminated due to slow accrual of patients. It was initially designed as a phase III trial with confirmed EDSS progression as the primary endpoint, which after an interim analysis was changed to a phase II trial with cumulative number

Table 1 Summary of reports of HSCT for MS

	n	MS subtype (n) RRMS	SPMS	PPMS	Age	Disease duration (years)	EDSS	Conditioning BEAM	Cy	Other	Follow-up time (months)	PFS Timepoint	Percentage	MRI Timepoint	Percentage	NEDA Timepoint	Percentage	TRM Percentage	Prognostic factors
Burman et al[37]	(41*) 48	34	5	2	31†	5.5‡	6‡	34	6		47†	60	77	60	85	60	68	0	Gd+ at baseline
Nash et al[40]	24	24			38‡	4.9‡	4.5‡	24			62‡	60	91	60	86	60	69	0	
Burt et al[38]	(145*) 151	118	27		37‡	61‡	4‡		145		30†	48	87	n/a	n/a	48	68	0	Disease duration <10 years RRMS vs SPMS fever in the peritransplant period
Atkins et al[39]	24	12	12		34‡	5.8‡	5‡			24	80‡	60	70	60	100	60	70	4.2	

*Only evaluated for safety.
†Mean.
‡Median.
EDSS, expanded disability status score; HSCT, haematopoietic stem cell transplantation; MS, multiple sclerosis; NEDA, no evidence of disease activity; TRM, treatment-related mortality; RRMS, relapsing-remitting MS SPMS, secondary progressive MS; PPMS, primary progressive MS; PFS, progression-free survival; BEAM, the combination of carmustine (BCNU), etoposide, cytarabine (Ara-c), and melphalan; n/a, not available; Cy, cyclophosphamide[40].

of new T2 MRI lesions as the primary endpoint. Patients were eligible for the study if they had clinically definite MS (RRMS or SPMS), an EDSS score between 3.5 and 6.5, a documented worsening in the previous year, and presence of one or more gadolinium-enhancing lesions on MRI despite conventional therapy. Only 21 patients were included, of whom only 7 were RRMS patients. Nevertheless, the investigators could report a significant reduction in the formation of new T2 lesions by 79% and a reduction in annualised relapse rate by 64% versus the active comparator, which was mitoxantrone. Mitoxantrone is a well-known drug with potent and well-described effects on clinical as well as MRI outcome measures.[42–45] The ASTIMS trial provides evidence for superior effect to an established drug that historically has been seen as the best option for treatment of aggressive MS.

Most of the clinical data on the effect on RRMS come from reports of uncontrolled single centres studies[38–40] or nationwide surveys,[37] containing in total 247 patients with MS, of whom 188 were RRMS patients. The inclusion criteria were slightly different between studies (see online supplementary appendix), but as a rule patients had failed one or more conventional therapies with EDSS progression and/or severe relapses. Only one study contained only RRMS patients,[40] and in some instances results from RRMS patients and patients with PPMS or SPMS were reported together. In addition, different conditioning regimens were used and patient selection varied. Nevertheless, clinical and radiological outcomes are fairly consistent between these case series.

Progression of disability

All studies reported on progression-free survival, defined as deterioration in EDSS by 0.5–1 point from baseline. Progression-free survival was 87% at 4 years[38] and 70%–91% at 5 years,[37 39 40] with the lowest numbers seen in cohorts containing a higher proportion of patients with SPMS. EDSS improved with 0.5–1.5 from baseline,[37 38 40] with the greatest improvement seen in the first year after HSCT, some additional improvement in the second year, and thereafter essentially stable levels of neurological function.[37 38]

Imaging

MRI provides important information about inflammation and to some extent neurodegeneration in MS. MRI event-free survival, defined as no appearance of new T2 lesions or gadolinium-enhancing lesions on T1 sequences, was 85%–86% at 5 years in two studies.[37 40] Of note, MRI event-free survival was 100% in patients treated with a high-intensity conditioning regimen, with follow-up time of more than 10 years in some patients.[39] One study reported that the mean volume of T2 lesions decreased from a pretransplant value of 15.69 cm^3 to 10.92 cm^3.[38] The rate of neurodegeneration is usually estimated by measurement of brain atrophy. Brain atrophy is more pronounced in patients with MS than in age-matched controls and may be further accelerated by HSCT. It has been associated with the use of busulfan-containing high-intensity conditioning regimens, which may be neurotoxic. Other possible explanations for this phenomenon include the resolution of disease-induced oedema ('pseudoatrophy') and continuous neurodegeneration of structures already damaged before HSCT.[46 47] Accelerated atrophy appears early after HSCT, subsides with time and eventually the brain atrophy rate reaches the levels of normal ageing, which is reassuring.[39 40 47]

No evidence of disease activity

Disease-free status, or no evidence of disease activity (NEDA), is an outcome measure that recently has gained considerable interest[48–51] and has become a treatment goal in clinical practice. NEDA is usually defined as the absence of new or enlarging T2 lesions or T1 gadolinium-enhancing lesions on MRI with no sustained EDSS score progression or clinical relapse.[48 52] Importantly, NEDA assessed early on predicts disability at long-term follow-up.[51] In an unselected group of patients, such as the Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women's Hospital cohort, NEDA was 7.9% at 7 years, even though a majority of patients were treated with standard disease-modifying therapy. Even with advanced immunotherapy, such as natalizumab or alemtuzumab, only 32%–39% maintained NEDA at 2 years in phase III clinical trials.[51] In contrast, 68%–70% of patients treated with HSCT maintained NEDA at 4–5 years after transplant.[37–40]

Quality of life

Patient-perceived health status and health-related quality of life (HRQoL) are measures of patients' condition and treatment outcome that have been increasingly recognised. In particular, MS is associated with a poor HRQoL, which deteriorates with disease progression, affecting family life, social functioning and employment status.[53] HRQoL assessment may be especially important in the evaluation of treatment with HSCT. Serious adverse events and impaired fertility may significantly reduce HRQoL. On the other hand, HSCT is a one-time procedure that potentially can reverse disability, which could improve HRQoL.

Two studies evaluated HRQoL before and after HSCT. One study used the 36-Item Short Form Survey (SF-36) instrument, where a change in five points or more is accepted as a clinically meaningful improvement. After a median follow-up time of 2 years, the SF-36 scores improved significantly by 19 points for total health (15 points for physical health and 20 for mental health).[38] In contrast, natalizumab and dimethyl fumarate failed to show clinically meaningful improvement in HRQoL on the SF-36 in the phase III trials.[54 55] In the second study HRQoL was evaluated with the Multiple Sclerosis Impact Scale (MSIS-29), where a change in eight points or more is considered clinically meaningful.[56] After 3 years, the investigators found that the median MSIS-29 score had improved by 15 points.[57] The MSIS-29 has seen less use than SF-36, but was employed to evaluate HRQoL in a postmarketing investigation of natalizumab in Sweden, but again the investigators failed to show a clinically meaningful difference.

Safety and adverse effects

Safety of the procedure has been a major concern, and historically HSCT has been viewed as a high-risk procedure. In a 2006 report from the EBMT register, a TRM of 5.3% in 183 examined patients was reported.[26] A high-intensity conditioning was associated with increased mortality and prolonged hospitalisation. In a later follow-up of EBMT data from 345 patients with MS, TRM had decreased to 3.8%. In a pooled analysis of patients with different autoimmune diseases, age <35 years and centre's experience were associated with lower risk of death (HR 1.7 for age and HR 2.5 for centre experience).[3]

With experience, better patient selection and refinement of the procedure, these numbers have improved significantly. In a recent meta-analysis TRM was 0.3% in procedures performed after 2005 and nil in patients treated with a low-intensity conditioning regimen.[58] To put these numbers in perspective, TRM

in phase II and III studies for alemtuzumab was 0.3%,[59–61] and the risk of contracting progressive multifocal leucoencephalitis in JC virus-positive patients treated with natalizumab is about 1% per year.[62]

Long-term side effects have been less studied. A common side effect is herpes zoster reactivation, which has been reported in 2.6%–26% of patients,[37–39] mainly dependent on the length of viral prophylaxis and the intensity of the conditioning regimen. This usually manifests as shingles, which is manageable with oral acyclovir. One concern is the development of secondary autoimmunity, such as thyroid disease, which occurs in 4.0%–17% of patients with MS after HSCT.[37–39] Idiopathic thrombocytopaenic purpura (ITP) after HSCT has also been reported in a few cases,[38 39] and therefore physicians should be on alert for these potentially serious adverse effects. The risk of development of malignancies and ovarian failure is unknown, but is likely related to the intensity of the conditioning regimen.

SUMMARY

Although head-to-head comparisons with other disease modifying drug (DMDs) are essentially lacking, available data suggest that HSCT for MS is superior to currently approved DMDs. The safety profile of the procedure has been improved in later years, and TRM is now on par with generally accepted procedures such as arthroplasty.[63] Other serious adverse events include secondary thyroid disease and ITP, occurring to a lesser degree than with comparable advanced forms of immunotherapy, such as alemtuzumab. In light of the above, the procedure could be recommended for RRMS patients with an unfavourable prognosis despite treatment with alternate approved therapy, who seek treatment at experienced centres. Current data suggest that the effect of HSCT in SPMS and PPMS is moderate at best, and further use should be limited to clinical trials.

NEUROMYELITIS OPTICA

NMO and NMO spectrum disorders (NMOSD) are autoimmune diseases of the CNS primarily affecting the optical nerves and spinal cord. The presence of IgG autoantibodies to water channel aquaporin-4 (AQP4-IgG) is highly specific for these conditions and potentially pathogenic.[64] The prognosis is poor due to respiratory failure and severe visual loss due to optic neuritis.[65] Treatment includes immunosuppressive and immunomodulatory drugs such as azathioprine and rituximab, but randomised controlled studies are lacking.

The use of autologous HSCT for treating NMO was first described in a 2010 case report.[66] The patient was a 23-year-old woman with a severe and rapidly disabling disease course: vision loss, paraparesis, dysaesthesia and radicular pain. Two years after disease onset, she was treated with HSCT using a BEAM conditioning regimen. At follow-up 12 months after the procedure, the patient was stable with no further relapses and normalised motor and sensory functions. Visual acuity had improved only slightly, but optic nerve atrophy was present before treatment.

In 2014 data from a retrospective multicentre study based on data from the European Group for Blood and Marrow Transplantation Autoimmune Diseases Working Party were presented.[67] Sixteen patients (13 women, 3 men) with NMO or NMOSD, refractory to other treatment, underwent autologous HSCT between 2001 and 2011. The median age at NMO diagnosis was 29 (range 10–56) and the median time from diagnosis to transplant was 2 years (range <1–17). The median EDSS at baseline was 6.5 (range 2–8.5) and 10/16 patients had AQP4-IgG at diagnosis. Nine patients were treated with an intermediate

BEAM-based conditioning regimen; the remaining seven patients had a lower intensity regimen based on Cy plus ATG or thiotepa-Cy alone. The median follow-up was 47 months (range 20–128). Thirteen patients (81%) had a relapse after a median of 7 months (range <1–57) and nine patients (56%) experienced progression of disability. The estimated relapse-free survival after 3 years was 31% (±12%) and after 5 years 10% (±9%); progression-free survival was 48% (±13%) after both 3 and 5 years. In total, three patients were stable and required no other treatment; the other 13 patients required further treatments after HSCT. One patient died from disease progression 14 months after HSCT. The serostatus of AQP4-IgG was unchanged in the eight AQP4-IgG seropositive patients, who were retested after HSCT.

Three of the patients who relapsed after autologous HSCT in the above-mentioned study were further treated with allogeneic HSCT, and the outcome of two of those patients (one man, one woman) was described by Greco et al in 2014.[68] Both patients reached clinical remission and improved in disability; EDSS had decreased from 6 to 3.5 and from 8.5 to 7.5 at follow-up after 4 and 3 years, respectively. No new relapses were observed, and in both patients the AQP4-IgG went from positive to negative after treatment.

Aouad et al[69] reported a single case of a 47-year-old woman with NMO and high titres of AQP4 antibodies who underwent autologous HSCT with a disease duration of 11 years. The patient was given two doses of rituximab, as a part of the conditioning regimen (Cy plus ATG). At follow-up 6, 9 and 12 months after treatment, AQP4-IgG could not be detected; she had no relapse, no clinical progression and no new lesions on MRI.

Currently available data suggest that autologous HSCT can reduce inflammatory activity in NMO in the short term, but a vast majority of patients will relapse within 5 years. Conditioning regimens containing rituximab and allogeneic HSCT may improve prognosis, although the few cases described prohibit any firm conclusions.

STIFF PERSON SYNDROME

Stiff person syndrome (SPS) is a rare autoimmune central nervous system disorder characterised by muscle stiffness and superimposed painful muscle spasms and frequently by the presence of antibodies against glutamic acid decarboxylase (GAD). Many patients respond to immune modulating therapy, but symptomatic treatment with GABAergic drugs such as benzodiazepines and baclofen may also be helpful. Sanders et al[70] reported two cases with severe anti-GAD positive SPS, who underwent HSCT with a high intensity conditioning protocol[70]. The follow-up time was 56 and 32 months respectively. Both patients achieved clinical remission with a return to premorbid function and neither experienced any unexpected serious adverse events. In one of the patients anti-GAD antibodies decreased from 127 U/mL before HSCT to 87 U/mL two months after the procedure.

Available data provide preliminary evidence that HSCT may be an effective therapeutic option in carefully selected cases of severe, treatment refractory SPS.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

CIDP is a disease targeting myelin in the peripheral nervous system. Approximately 80% of patients will respond adequately to first-line treatment,[71] but of those 12%–29% eventually become treatment-refractory.[72][73] If not treated efficiently secondary axonal loss will accumulate over time, increasing the level of morbidity and risk of mortality.[74] Severe disability despite treatment is seen in 13% of patients and mortality rates vary between 4% and 17%, mainly due to respiratory failure or pulmonary embolism.[72][75] Treatment-refractory patients with CIDP are usually treated with second-line immunomodulatory drugs such as cyclophosphamide, ciclosporin, rituximab, azathioprine and methotrexate, although evidence for the efficacy of these treatments is lacking.[76][77]

The use of autologous HSCT in treatment-refractory CIDP was first reported in 2002 by Vermuelen and Van Oers[31], who used a BEAM conditioning protocol. The response was maintained until 5 years post-transplant when symptoms recurred.[78] This initial report has been followed by mainly case reports of up to three patients,[79–82] with one notable exception. In the as of yet largest documented series of patients with CIDP receiving HSCT, Press et al[83] described 11 patients refractory to first-line treatment, and in 10 of them also to one or more second-line treatments. They received HSCT at four different university hospitals in Sweden between 2002 and 2012. The total Inflammatory Neuropathy Cause and Treatment (INCAT) scale and Rankin scores improved significantly within 2–6 months after HSCT and continued to do so at last follow-up. The motor action potential amplitudes improved rapidly within 4 months after the procedure. Eight of the 11 patients maintained drug-free remission at last follow-up after HSCT, and only three patients experienced a relapse. The procedure was generally speaking safe with no TRM, but adverse events included asymptomatic and symptomatic cytomegalovirus and Epstein-Barr virus reactivation, haemorrhagic cystitis and pancreatitis. Of note, one of these patients received HSCT twice due to a post-HSCT relapse. After the second HSCT the patient had a 3-month episode of fever, bronchitis and elevated liver enzymes probably related to Epstein-Barr and cytomegalovirus reactivation.[84]

Bregante et al[85] described a patient with Sjögren's syndrome-associated CIDP, who first responded to HSCT, but got a relapse after 6 months, which was treated successfully with allogeneic HSCT. The patient also developed aplastic anaemia at the time of the neurological relapse.

We could identify reports containing in total 20 patients with treatment-refractory CIDP receiving HSCT at 10 different centres (table 2). Four were treated with the intermediate-intensity BEAM conditioning regimen, and the remainder with low-intensity cyclophosphamide-based protocols. Ninety per cent of the patients improved after the procedure, and 35% experienced a relapse. The most common adverse events (apart from the expected adverse events related to acute toxicity) were asymptomatic and symptomatic cytomegalovirus and Epstein-Barr virus reactivation.

These published cases, which include our own experiences, suggest that HSCT may be a treatment that may induce long-term remission even in severe treatment-refractory cases of CIDP with an overall acceptable risk profile. To improve outcome, treatment should preferably be initiated before irreversible axonal damage has occurred. A more precise estimation of the clinical efficacy of HSCT for CIDP will require a randomised controlled trial.

OTHER PERIPHERAL NEUROPATHIES

Antimyelin-associated glycoprotein (MAG) neuropathy is an antibody-mediated demyelinating neuropathy clinically characterised by distal, symmetric, predominantly sensory symptoms. Immunomodulating therapies are often tried, but there is insufficient evidence for their effect.[86] In the report by Mahdi-Rogers

Table 2 Summary of reports of HSCT for CIDP

	n	Age at onset	Gender	Disease duration (months)	Conditioning	Clinical outcome	Duration of follow-up (months)	Relapse (months after HSCT)
Vermeulen et al[31 78]	1	38	M	120	BEAM	Good recovery, but still on prednisone 5 mg/day and relapse after 5 years	>60	60
Kamat et al[82]	2	42	M	24	Cy+ATG	Unable to walk to ambulant	18	None
		72	M	120	Cy+ATG	Stabilised	3	None
Oyama et al[79]	1	32	F	30	Cy+ATG	Rankin functional score from 4 to 1	22	None
Barreira et al[81]	1	24	M	144	Cy+ATG	Short transient response	2	1
Mahdi-Rogers et al[80]	3	29	F	252	Cy+ATG	MRC sum score 39–48–29	26	18
		58	F	156	Cy+ATG	MRC sum score 58–62	6	None
		72	M	72	Cy+ATG	MRC sum score 46–34	19	None
Axelson et al[84]	1	56	M	11	Cy	INCAT score from 10 to 2	101	25
				36	Cy+ATG	INCAT score from 6 to 2		None
Press et al[83]	11	16–67	10 M, 1 F	11–228	CY+ATG (7)	Median INCAT score from 6 to 1	6–101	23
					BEAM (3)			14
					Melphalan (1)			14
Bregante et al[85]	1	24	M	7	Thiotepa+Cy+G-CSF	Wheelchair users to ambulant for 6 months to unable to walk	60	6
					Fludarabin+Cy+TBI*	Unable to walk to ambulant		None

*Allogeneic HSCT.
ATG, antithymocyte globulin; CIDP, chronic idiopathic demyelinating polyneuropathy; HSCT, haematopoietic stem cell transplantation; TBI, total body irradiation; BEAM, the combination of carmustine (BCNU), etoposide, cytarabine (Ara-c), and melphalan; Cy, cyclophosphamide; G-CSF, granulocyte colony stimulating factor; MRC, Medical Research Council Scale for Muscle Strength; INCAT, 'Inflammatory Neuropathy Cause and Treatment Scale.

et al mentioned above,[80] the authors also described a patient with demyelinating polyneuropathy with IgM paraproteinaemia and MAG antibodies who first improved after HSCT, but relapsed after 30 months.

Multifocal motor neuropathy (MMN) is an uncommon immune-mediated, slowly progressive, purely motor neuropathy that is characterised by the presence of multifocal conduction blocks in motor nerves and frequently serum anti-GM1 antibodies. IVIg is to date the only therapy with proven efficacy providing transient improvement in muscle strength. A single report describes a patient with MMN who responded to IVIg but had no benefit from treatment with HSCT using a low-intensity conditioning regimen.[87]

The POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes) is a paraneoplastic disorder secondary to a plasma cell dyscrasia. The efficacy of HSCT in POEMS syndrome reported in case series has been mainly been based on haematological criteria, and clinical recovery of peripheral neuropathy has not always been specifically evaluated.[88] It is beyond the scope of this article to review the extensive literature on HSCT in POEMS syndrome describing more than 100 cases, and the interested reader is instead referred to the recent reviews in the field.[89 90]

MYASTHENIA GRAVIS
MG is neurological disease with immune reactivity against the postsynaptic endplate of the neuromuscular junction.[91] Apart from symptomatic treatment with cholinesterase inhibitors, many patients also require immunomodulatory treatment. The prevalence of treatment-refractory MG has been estimated to be 10% of patients with generalised disease.[92 93]

The use of autologous HSCT in MG was first reported in 2004 by Burt et al,[32] who employed a low-intensity conditioning regimen. The patient, a 30-year-old woman with severe therapy-resistant anti-muscle specific kinase (MUSK) antibody positive MG (Osserman grade IIB/III), was free from symptoms

(Osserman grade 0) 2 months after HSCT, and prednisolone could be tapered after 4 months. There were no HSCT-related adverse events during the 6-month follow-up.

Bryant et al[94] reported seven cases of severe MG treated with HSCT. Six patients underwent HSCT for MG and one for follicular lymphoma with coincident active MG. Mean ages at MG diagnosis and at HSCT were 37 (±11) and 44 (±10) years, respectively. Five patients had acetylcholine receptor antibodies and two were seronegative. MG severity was graded as moderate (grade III) to life-threatening (grade V) by the Myasthenia Gravis Foundation of America (MGFA) clinical classification, and patients were refractory to treatments including pyridostigmine, corticosteroids, additional immunomodulators and plasma exchange or IVIg. Four patients had previously undergone thymectomy; none had thymoma. All patients received high-intensity conditioning regimens containing TBI or busulfan, leading to durable remission with no residual MG symptoms and freedom from ongoing MG therapy in all patients. The median follow-up was 40 months (range 29–149 months). Acetylcholine receptor antibodies were not analysed after HSCT. Three patients experienced transient viral reactivations and one developed a secondary autoimmune disease after HSCT, all of which resolved or stabilised with treatment.

Håkansson et al[95] described a patient with severe MG, diagnosed at the age of 26, refractory to corticosteroids, four oral immunosuppressants, cyclophosphamide, rituximab and bortezomib. At the age of 63, she was treated with HSCT with the intermediate BEAM conditioning regimen. At follow-up 2 years after the procedure, the patient had significantly improved in objective tests (MG composite score decreasing from 64 to 6). Diplopia was her only remaining symptom and she was off all medications for MG. Interestingly, acetylcholine receptor antibodies were still detectable after HSCT. No serious adverse events were reported.

A single report of one patient with intractable MG undergoing allogeneic HSCT describes a treatment-free remission with minor

residual symptoms at 40 months after transplantation.[96] The role of allogeneic HSCT in a disease as MG should be limited due to its high risk of mortality and the possible occurrence of secondary MG as a manifestation of graft versus host disease.

Available data provide preliminary evidence that HSCT can be an effective therapeutic option in carefully selected cases of severe, treatment-refractory MG.

CONCLUDING REMARKS

In this review, we have summarised the past 20 years of experience with autologous HSCT for neurological diseases. The vast majority have been patients with MS, and by now more than 1000 individuals have been treated with this procedure. Available data are very consistent on 'no evidence of disease activity', and 68%–70% of RRMS patients will remain in NEDA 5 years after HSCT regardless of conditioning regimen. Safety has been improved and the TRM has been estimated at 0.3% in the last decade. These numbers compare favourably with conventional treatment and open up for a more widespread use. Although considerably fewer patients with MG and inflammatory neuropathies have been treated so far, the reported outcome looks promising and should be followed by formalised clinical trials. Meanwhile, the procedure could be considered in patients with severe treatment-resistant disease. In contrast, HSCT does not seem to be able to contain disease activity in NMO, and further use outside of clinical trials is questionable at best.

REVIEW CRITERIA

A search for original articles was performed in Medline and PubMed. The search terms 'multiple sclerosis', 'neuromyelitis optica', 'chronic inflammatory demyelinating polyneuropathy', 'multifocal motor neuropathy', 'inflammatory neuropathy', 'peripheral neuropathy', 'myasthenia gravis', 'hematopoietic stem cell transplantation', 'relapsing-remitting' and 'clinical trial' were used alone or in combination. The reference lists of identified articles were scrutinised for further relevant papers.

For efficacy in MS, we included only those reports that included at least 50% RRMS patients and reported the outcome of at least 10 patients. Four studies were found using this strategy. In addition, we included the only randomised controlled trial that was identified, although it mainly contained data on SPMS patients.

For NMO we included all relevant reports found using this strategy.

For SPS we included all relevant reports found using this strategy.

For CIDP and other inflammatory polyneuropathies we included all relevant reports found using this strategy.

For MG we included all relevant reports found using this strategy.

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