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Chapter 11

tit0010 # Hematopoietic stem cell transplantation for multiple sclerosis: improving understanding and addressing misconceptions

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Abstract

Autologous hematopoietic stem cell transplantation (HSCT) for multiple sclerosis (MS) is the technique of administrating a short immunosuppressive regimen over 4–6 days (depending on the drug regimen) followed by intravenous infusion of one's own hematopoietic stem cells to hasten hematopoietic recovery. The toxicity and efficacy of the procedure depend on the regimen and on patient selection and, to a lesser extent, on center experience. MS-specific nonmyeloablative regimens are less toxic and safer than myeloablative regimens that were initially developed for cancer. To date, there have been no randomized trials comparing the different regimens. HSCT like all immune-based therapy is more effective for the inflammatory phase of MS. It is effective for relapsing-remitting MS, less effective for active secondary progressive MS (SPMS), and almost ineffective for nonactive SPMS and primary progressive MS. Effectiveness and superiority of HSCT have been reported in a phase III randomized trial against the best available disease-modifying therapies at that time (mostly natalizumab) and in large meta-analyses. Compared to disease-modifying therapies, HSCT demonstrates posttransplant drug-free meaningful improvement of neurologic disability and quality of life for prolonged long-term follow-up in most patients.

s0010 ## INTRODUCTION

p0050 Initially developed from animal models performed in the 1990s, hematopoietic stem cell (HSC) transplantation (HSCT) for multiple sclerosis (MS) has significantly evolved over the last few years. Nonrandomized trials, large meta-analyses, and a randomized controlled trial have proven its effectiveness, but most neurologists and most hematologists do not have clinical experience with HSCT and MS, respectively. Additionally, the acronyms disease-modifying therapy (DMT) used by neurologists and HSCT used by hematologists are imprecise terms that for the nonspecialist can be misleading. Herein, we will discuss MS, compare DMT to HSCT, offer a more precise terminology for both DMT and HSCT, and discuss development of and different types of HSCT for relapsing-remitting MS (RRMS).

EPIDEMIOLOGY

MS is the most common immune-mediated neurologic disease of early adulthood (Reich et al., 2018). While MS is most common in young and middle-aged adults, approximately 3% of MS cases are early-onset also known as pediatric-onset MS with diagnosis under age 18 (Chitnis et al., 2009; Mirmosayyeb et al., 2020). Early-onset MS has more frequent relapses but slower progression of disability (Chitnis et al., 2009; Mirmosayyeb et al., 2020). Roughly 9% of MS patients are late-onset MS defined as presenting at age 50 or later (Noseworthy et al., 1983; Mirmosayyeb et al., 2020). Late-onset MS has fewer relapses but faster accumulation of disability (Noseworthy et al., 1983; Mirmosayyeb et al., 2020). MS affects approximately 3 million people worldwide (Reich et al., 2018). Prevalence is 2–3 times higher in women

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than men (Hittle et al., 2023). Distribution by race is predominately Caucasian followed by African American and Hispanic (Amezcua and McCauley, 2020). It occurs less frequently in Asians and indigenous peoples of the Americas (Robers et al., 2023; Zhang et al., 2023).

p0060 The etiology of MS is unknown. It is associated with multiple factors including genetic background, for example, human leukocyte antigen locus, smoking, latitude, vitamin D levels, ultraviolet (UV) light exposure, and certain viruses. The risk of MS increased in people with major histocompatibility complex HLA-DRB1*15:01, (Williamson et al., 2013; s0020 Menegatti et al., 2021). The risk of developing MS may be p0070 related to linkage of HLA-DRB1 with tumor necrosis factor α as both are in proximity to each other on human chromosome 6 (Williamson et al., 2013). Cigarette smoke generates reactive oxygen species promoting inflammation and damage to the vascular endothelial blood–brain barrier (Handel et al., 2011; Seo et al., 2017). MS and lower vitamin D levels are more frequent at higher latitudes and lower UV light exposure (Acheson et al., 1960; Webb et al., 1988; Munger et al., 2006; Simpson et al., 2019). Since 1990, the department of defense has maintained a serum repository for disease surveillance (Rubertone and Brundage, 2002). One sample is collected upon enrollment of a recruit and every 2 years thereafter (Rubertone and Brundage, 2002). For patients with MS, the average time from the first sample until onset of MS was 5.3 years (range 1–13 years) (Munger et al., 2006). Using these pre-MS samples, the risk of MS for Caucasians compared to controls who did not develop MS was increased when predisease serum 25-hydroxyvitamin D levels were less than 100 nmol/L (Munger et al., 2006). Latitude and UV-B light (290–3125 nm) affect Vitamin D levels (Acheson et al., 1960; Webb et al., 1988; Simpson et al., 2019). At higher latitudes and low light winter months, most UV-B light is absorbed by the atmosphere (Acheson et al., 1960; Webb et al., 1988; Simpson et al., 2019). In the absence of UV-B light, human keratinocytes in the epidermis are unable to metabolize 7-dehydrocholesterol into previtamin D3 (Webb et al., 1988). A latitude effect on risk of MS is observed for both northern and southern hemispheres (Sabel et al., 2021).

p0065 In the 1970s, measles was suspected to be associated with MS because of high cerebrospinal fluid measles antibody indices in patients with MS (Norrby et al., 1974). In the 1990s, human herpes virus 6 (HHV-6) was suspected because HHV-6 deoxyribonucleic acid was detected in MS plaques p0075 (Challoner et al., 1995). In 2000, emphasis shifted to Epstein–-Barr virus (EBV) when it was reported that CSF oligoclonal bands in 5 of 15 MS patients recognized EBV nuclear antigen 1 (Rand et al., 2000). In a 2022 study, using samples from the DODSR, 35 of 801 military recruits who developed MS were EBV seronegative when enrolling into the military (Bjornevik et al., 2022). Conversion to EBV seropositive occurred in 34 of 35 before being diagnosed with MS (Bjornevik et al., 2022). The median time from EBV seroconversion to onset of MS was 5 years (range 0–10 years) (Bjornevik et al., 2022). Limitations to this study are that seroconversion may be an epiphenomenon from close quarters spread of a common aerosolized highly infectious agent (Dowd et al., 2013). EBV DNA is not present in MS plaques (Hilton et al., 1994), and in patients with MS, the prevalence of EBV DNA in the serum is less than 1.8% compared to 8.9% for HHV-6 (Pereira et al., 2023). On the other hand, HLA-DRB1*15:01 that is a risk factor for MS is a coreceptor for EBV (Menegatti et al., 2021).

PATHOLOGY

MS commonly begins with perivascular breakdown of the blood–brain barrier and extravasation of immune cells including T cells (CD8 > CD4), B cells, and macrophages into CNS parenchyma (Ortiz et al., 2014; Romeo and Segal, 2023). Breakdown in the blood–brain barrier usually occurs around small venules located in periventricular and subcortical areas in the cerebrum, in the middle cerebral peduncle that connects the pons to the cerebellum in the posterior fossa, and in the posterior columns of the spinal cord (Ortiz et al., 2014). After perivascular leak of these immune cells, lesions or plaques develop that are marked by a dynamic interaction of T and B lymphocytes, plasma cells, macrophage-mediated stripping of myelin, and attempts at remyelination and repair (Raine and Scheinberg, 1988; Trapp et al., 1998; Frischer et al., 2015). Acute lesions are characterized by a center of predominately macrophage-mediated myelin disintegration, oligodendrocyte apoptosis, and demyelinated axons (Absinta et al., 2021). Chronic lesions may be either active (chronic active lesion, CAL) or silent (inactive lesion) and have a relatively hypocellular center in which oligodendrocytes and neurons are replaced by astrocytes, a process called astrogliosis (or gliosis) (Prineas et al., 2001). CAL are chronic smoldering lesions (Absinta et al., 2019). The surrounding rim contains complement deposition with activated iron-laden microglia and macrophages (Lassmann, 2018). On imaging CAL present as nongadolinium-enhancing lesions with paramagnetic rims (Absinta et al., 2019). The periphery of a CAL also contains occasional CD8 and $CD4^+$ T cells, plasma cells, plasmablasts, and dendritic cells (Lassmann, 2018). Inflammation and demyelination continue at the borders of a CAL. In chronic silent lesions, the borders are sharp without immune cells or iron-laden macrophages or microglia and without ongoing inflammation or demyelination (Lassmann, 2018).

It is from these chronic lesions in which the normally soft brain tissue is replaced with gliosis or scarring for which this disease first acquired its name “sclérosis en plaque disseminée” by the French physician Jean Martin Charcot (1825–93) (Bernard, 2018). The French still refer to MS as “sclerosis en plaque.” The English-speaking world modified this term to MS meaning “multiple hard scars.” Coincident with demyelination, neuronal damage occurs in both acute lesions and CALs. Injury to an axon that conducts nerve

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p0090 impulses manifests as transection that abruptly terminates with stumps or bulbs referred to as axonal ovoids (Trapp et al., 1998). Axonal ovoids are most prevalent in acute lesions, where they are present at roughly 11,000/mm^3. They are still present in CALs, albeit at a smaller number, 3000/mm^3 (Trapp et al., 1998). In comparison, normal brain white matter demonstrates on average one axonal ovoid per sample (Trapp et al., 1998). Axonal transection with attempts to resprout axons is a consequence of demyelination that begins in an acute active lesion and continues in the periphery of CALs. In addition, there is a slow burning, ongoing axonal p0095 destruction, which can be seen even in inactive demyelinated plaques, in which inflammation is sparse or absent. Such ongoing axonal injury is lacking in remyelinated shadow plaques (Lassmann, 2003). MS is both an inflammatory demyelinating and neuronal degenerative disease of the CNS.

s0025 IMMUNOLOGY

p0080 T cell involvement in MS is supported by peripheral blood T cells reactive to myelin epitopes (Wang et al., 2004; Kaskow and Baecher-Allan, 2018), dysfunctional T regulatory (Treg) cells (Goverman, 2021), skewed T cell receptor repertoire in the peripheral blood of patients with MS (Muraro et al., 2005), and clinical response to T cell-specific immune-suppressive drugs.

p0100 B cell involvement in MS is supported by myelin antigen presentation by B cells (Zamvil and Hauser, 2021), skewed CSF oligoclonal immunoglobulin IgG bands that recognize ubiquitous intracellular self-proteins (Brandle et al., 2016), antigen-specific interaction, and coactivation between B and T cells (Lanzavecchia, 1985; Jelcic et al., 2018), and clinical response to anti-B cell-specific monoclonal antibodies. Both T and B cells release cytokines and chemokines that contribute to macrophage and microglia activation leading to phagocytosis of myelin protein (Lassmann, 2018). Demyelinated axons, reactive oxygen species, and inflammatory cytokines contribute to axon transection (Lassmann, 2018). Astrocytes gradually complete the insult by releasing further cytokines and functioning as fibroblast-like cells that replace oligodendrocytes and neurons within CNS plaques (gliosis) (Sofroniew, 2009).

s0030 DIAGNOSIS OF MULTIPLE SCLEROSIS

p0085 s0035 The diagnosis of MS is currently determined by the revised McDonald criteria initially proposed in 2001 (McDonald et al.,

p0105 2001) and modified in 2005 (Polman et al., 2005), 2010 (Polman et al., 2011), and 2017 (Thompson et al., 2018). The underlying principle of the McDonald criteria are two or more inflammatory events disseminated in time and space. Disseminated in time is present if two relapses have occurred at least 1 month apart from each other. A relapse is defined as neurologic deficits or symptoms lasting more than 24 hours and not related to an infection. DIS means symptoms and findings that can be attributed to different lesions in the brain or spinal cord or magnetic resonance imaging (MRI) lesions occurring in different places in the brain or spinal cord.

The original 2001 and 2005 McDonald criteria required many more than two brain lesions for documentation of DIS (McDonald et al., 2001; Polman et al., 2005). This was simplified in the 2010 McDonald MRI criteria to coincide more closely with two different areas in the brain defined as one or more T2 MRI lesions in at least two of the following areas: periventricular, juxtacortical, infratentorial, or spinal cord (Polman et al., 2011). While more sensitive for diagnosing MS than the earlier imaging DIS criteria, numerous DIS lesions on MRI confined to only one area (e.g., periventricular) would not meet the 2010 MS criteria for DIS.

The revised 2017 criteria were modified to increase sensitivity by accepting only one MRI lesion provided a second clinical attack corresponded to a separate area of the brain (Thompson et al., 2018). The 2017 criteria also allowed for just one clinical attack provided that the CSF was positive for oligoclonal bands because they are indicative of a high risk for a second attack (Thompson et al., 2018). Detection of MS by the 2017 criteria increased diagnostic sensitivity to 100% (range 87%–100%) but decreased specificity to 13.8% (range 4%–32%) (Gobbin et al., 2019). A problem with defining MS by MRI is that no single demyelinating CNS lesion is pathognomonic for MS. Even a patent foramen ovale or migraine headaches may cause one or more T2 lesions (Mariotti et al., 2012; Bashir et al., 2013; Signoriello et al., 2018).

While not included in the current McDonald's criteria, a central vein sign has been suggested as a diagnostic marker for MS (Sinnecker et al., 2019; Cagol et al., 2023). The central vein sign is a venule located in the center of a demyelinating lesion. Small CNS venules are pathologically located within classic MS T2 lesion locations, that is, periventricular, juxtacortical, infratentorial, and spinal. Most clinical MRI scanners utilize a less discerning 1.5 Tesla (1.5 T) magnetic field strength. Optimal visualization and detection of the central vein sign would require a 3 T or if available a 7 T magnetic field strength and thin image slices (1 mm) instead of the standard 3–5 mm thick MRI slices (Kollia et al., 2009). While the McDonald criteria are being continually refined, the definition of an inflammatory attack (relapse) may require a more refined definition as will be discussed later under progression independent of relapse activity (PIRA).

SUBTYPES OF MULTIPLE SCLEROSIS

From onset, the pathophysiology of MS is both an immune-inflammatory and neuronal-degenerative process. Different stages or subtypes of MS (Fig. 11.1) are predominately inflammatory or degenerative (Lublin et al., 2014). Clinically isolated syndrome (Miller et al., 2012) and RRMS are predominantly inflammatory (Lublin et al., 2014). Clinically isolated syndrome is defined as the first clinical presentation of CNS demyelination that does not yet meet the McDonald criteria for dissemination in time and space (Miller et al., 2012). An isolated radiological presentation of demyelination without clinical symptoms is called radiologically isolated

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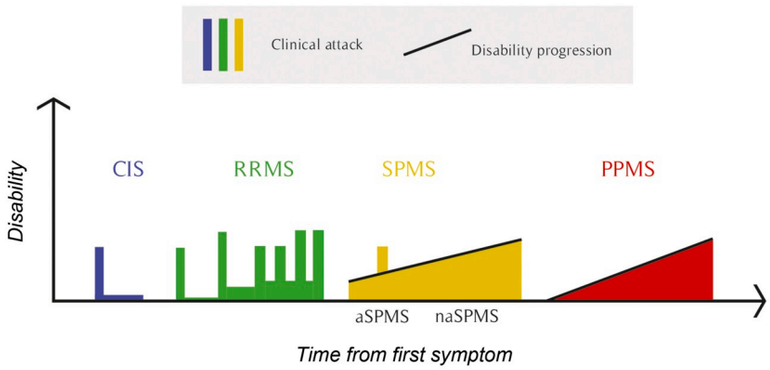

f0010 **Fig. 11.1.** Subtypes of multiple sclerosis. *aSPMS*, active SPMS, *CIS*, clinically isolated syndrome, *naSPMS*, nonactive SPMS, *RRMS*, relapsing-remitting multiple sclerosis, *PPMS*, primary progressive multiple sclerosis, *SPMS*, secondary progressive multiple sclerosis.

syndrome and is not yet considered a subtype of MS (Hosseiny et al., 2020). RRMS is the most common presentation of MS and fulfills the McDonald criteria for DIS and disseminated in time (Lublin et al., 2014). Following recovery from an acute attack, the neurologic baseline may or may not be worse, but neurologic function remains stable between acute attacks (Fig. 11.1).

p0110 p0120 Progressive accumulation in baseline disability without relapses or between relapses indicates a shift in pathophysiology toward predominate neurodegeneration (Fig. 11.1) (Filippi et al., 2021). After an initial course of RRMS, progressive neurologic decline defined as secondary progressive MS (SPMS) may occur without new attacks (clinical or radiological) defined as nonactive SPMS or may occur between attacks defined as active SPMS (Lorscheider et al., 2016; Inojosa et al., 2021; Ziemssen et al., 2022). Primary progressive MS (PPMS) has baseline progression from onset of symptoms without a preceding RRMS interval (Lublin et al., 2014). Active PPMS has baseline progression from onset and occasional or rare relapses/radiological activity (Lublin et al., 2014). The prevalence of spinal cord or brainstem involvement is greater in both SPMS and PPMS compared to RRMS (Filippi et al., 2000). Identifying MS subtype is important for directing therapy. All current therapies for MS whether DMT s0045 or autologous HSCT are based on immune modulation, suppression, or reset (Yang et al., 2022). Immune-based therapies p0125 including HSCT show efficacy for clinically isolated syndrome or RRMS, are significantly less effective for active SPMS or active PPMS and are ineffective for nonactive SPMS or PPMS (Manouchehri et al., 2022; Yang et al., 2022). Results of all immune-based treatments including DMTs and HSCT will significantly differ whether the type of MS is RRMS or SPMS.

s0040 p0130 DISEASE-MODIFYING THERAPIES AND HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR RELAPSING-REMITTING MULTIPLE SCLEROSIS

p0115 The terms “DMT” and “HSCT” are imprecise terminology developed in different medical disciplines, that is, neurology and hematology, respectively. Pharmaceutical drugs are often referred to as DMTs, usually describing a category of treatments designed to alter the natural course of a disease. However, the term “DMT” does not clarify what aspect of the disease is being modified. Do these treatments modify relapses, disability progression, quality of life (QOL), or something else, such as no evidence of disease activity (NEDA-3) which is based on absence of relapses, progression, or no new or enlarging MRI lesions?

The word autologous HSCT implies that HSCs are therapeutic or disease-modulating. In autologous HSCT, efficacy comes from the immune-suppressive or immunoablative drugs used in the conditioning regimen and not from HSCs. Unmanipulated autologous HSCs are a homologous blood product similar to an autologous red blood cell (RBC) unit collected before and transfused during or after a surgical procedure. Autologous HSCT should be regarded as an immune-based DMT. To bridge the gap in understanding between neurology and hematology, autologous HSCT regimens for RRMS that have completed a randomized trial as well as other regimens in use will be compared to and contrasted with pharmacology drugs from randomized DMT trials for RRMS.

Mildly effective disease-modifying therapies: relapse-slowing therapy

There are two classes of mildly effective DMTs, interferon (IFN) and glatiramer acetate (GA) that are referred to as injectable DMTs because they are administered subcutaneously or intramuscular. One mildly effective DMT (teriflunomide) is taken orally (Table 11.1). Mildly effective DMTs are in general relapse-slowing therapy although some individuals with milder diseases will respond well, and for them, it will be a relapse-stopping therapy and possibly also a disability-stopping therapy.

In the 1950s, it was noted that infection of cells with an inactivated or dead virus caused the cells to secrete a substance into the media that would interfere with live viral infection of other cells (Taylor, 2014). This interfering factor was later named IFN (Taylor, 2014). The cloning and expression of the IFN gene in mammalian cells allowed access to large amounts of IFN in the supernatant that could be purified and used for clinical trials (Taylor, 2014). IFNs are

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t0010 ***Table 11.1***

Disease-modifying therapies for relapsing-remitting multiple sclerosis.

Drug(s) for disease-modifying therapy for RRMS	Route	Randomized trial
Mildly effective DMT – relapse-slowing therapy		
IFN β-1b – Betaseron, Extavia	SC, QOD	BENEFIT (Kappos et al., 2016)
IFN β-1a – Avonex	IM, weekly	MSCRG (Jacobs et al., 1996)
IFN β-1a – Rebif	SC, TIW	PRISMS (Ebers, 1998)
Peg IFN β-1a – Plegridy	SC, Q2 weeks	ADVANCE (Calabresi et al., 2014a)
Glatiramer acetate – Copaxone	SC daily, TIW	GALA (Berger, 2000)
Teriflunomide – Aubagio	PO daily	TEMSO (Comi et al., 2019)
Moderately effective DMT – short-term disability-slowing therapy		
Fingolimod – Gilenya	PO daily	FREEDOMS (O'Connor et al., 2011)
Siponimod – Mayzent	PO daily	EXPAND (Subei and Cohen, 2015)
Ponesimod – Ponvory	PO daily	OPTIMUM (Calabresi et al., 2014b)
Ozanimod – Zeposia	PO daily	SUNBEAM (Cree et al., 2022)
Dimethyl fumarate – Tecfidera	PO BID	DEFINE (Gold et al., 2012)
Dioximel fumarate – Vumerity	PO BID	EVOLE (Wray et al., 2022)
Daclizumab – Zinbryta (removed from the market)	SC monthly	SELECT (Gold et al., 2013)
Highly effective DMT – Disability-slowing therapy		
Cladribine – Mavenclad	Two cycles yearly	CLARITY (Giovannoni et al., 2010)
Mitoxantrone – Novantrone	IV q 3 months	MIMS (Hartung et al., 2002; Millefiorini et al., 1997)
Natalizumab – Tysabri	IV q 4–6 weeks	AFFIRM (Havrdova et al., 2009), SENTINEL (Radue et al., 2010)
u0020 Alemtuzumab – Lemtrada, CAMPATH	IV × 5 days year 1	CARE MS1 (Warner and Arnason, 2012)
u0025	IV × 3 days year 2	CARE MS2 (Cohen et al., 2012)
Ocrelizumab – Ocrevus	IV q 6 months	OPERA 1 (Hauser et al., 2008)
Ofatumumab – Kesimpta	SC weeks 0, 1, 2, q month	ASCLEPIOS (Hauser et al., 2017)
Nonmyeloablative HSCT – disability-reversing therapy		
Cyclophosphamide/rabbit antithymocyte globulin – Cytoxan/rATG	IV – cytoxan × 4 days, ATG × 5 days	MIST (Burt et al., 2009)

ATG, antithymocyte globulin; *BID*, bis in die (twice a day); *Cytoxan*, cyclophosphamide; *DMT*, disease modifying therapy; *IM*, intramuscular; *IFN*, interferon; *IV*, intravenous; *MS*, multiple sclerosis; *PO*, per os (oral); QOD, every other day, *RRMS*, relapsing-remitting multiple sclerosis; *SC*, subcutaneous;; *TIW*, three times a week.

cytokines normally released by immune cells to block viral infectivity and modulate immune cell responses (Taylor, 2014). Treatment of MS with IFN-γ exacerbated MS flares (Panitch et al., 1987). Treatment with IFN-ß had the opposite effect and ameliorated flares (Goldschmidt and Hua, 2020).

p0135 IFN-ß reduces matrix metalloproteinase (MMP)-9 and very late antigen (VLA)-4 expression and in doing so it counteracts IFN-γ-

p0145 induced extravasation of immune cells across the blood–brain barrier (Muraro et al., 2000; Minagar et al., 2003). Treatment with IFN-β (e.g., Betaseron, Extavia, Avonex, Rebif, and Plegridy) in trials, such as BENEFIT (Kappos et al., 2016), MSCRG (Jacobs et al., 1996), PRISMS (Ebers, 1998), and ADVANCE (Calabresi et al., 2014a) decreased MS relapses but did not slow accumulation of disability (Table 11.2).

p0140 The main side-effects of IFNs (Table 11.3) are influenza-like symptoms of myalgias, aching, fever, chills, and headache, and more rarely idiopathic thrombocytopenic purpura (ITP), hypo–hyperthyroidism, hepatic toxicity, leukopenia, and injection site reactions. Over time many patients develop neutralizing antibodies that prevent effectiveness. For all causes, 37% and 56% of patients discontinue IFNs by 1 and 3 years, respectively (Sabido-Espin and Munschauer, 2017).

GA (Copaxone) is a mixture of four amino acids present in myelin basic protein. The ability of self-epitopes, such as myelin basic protein to induce an inflammatory immune response depends upon costimulation which requires an adjuvant. When a self-peptide is injected without an adjuvant no inflammatory costimulation occurs which shifts the immune system toward tolerance to those peptides (Teitelbaum et al., 1971). T helper (Th) cells may be either Th1 that secrete proinflammatory interleukins (IL) and cytokines, such as IL-2,

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t0015 *Table 11.2*

Mechanism of action of disease-modifying therapies for relapsing-remitting multiple sclerosis.

Drug(s) for disease-modifying therapy of RRMS	Predominant mechanism of action on immune system
Mildly effective DMT – relapse-slowing therapy	
u0030 Interferon β1b, 1a (IFN) – Betaseron, Avonex, Rebif, Plegridy	T cell cytokine profile – increases IL-10.
u0035	T-cell trafficking – decreases MMP-9 and VLA-4
Glatiramer acetate – Copaxone	T cell cytokine profile – increases Th2 cells
Terifluomide – Aubagio	T- and B-cell proliferation and activation
Moderately effective DMT – short-term disability-slowing therapy	
Sphingosine 1 phosphate (S1P) receptor inhibitor or modulator – Gilenya, Mayzent, Ponvory, Zeposia	T- and B-cell trafficking, atrial arrhythmias, macular edema, HA, hepatotoxic, back pain, HTN, orthostatic hypotension, UTI, dizziness, anxiety, and dyspnea
Fumarates – Tecfidera, Vumerity	T cell cytokine profile – increases Th2 cells and antioxidant effect via nuclear factor erythroid factor2-related factor 2 (Nrf2)
Daclizumb – Zinbryta	Binds CD25, the α subunit of T cell IL-2 receptor
Highly effective DMT – disability-slowing therapy	
Cladribine – Mavenclad	Reduction of T and B cells due to disruption of DNA synthesis and repair
Mitoxantrone – Novantrone	Reduction of T and B cells by intercalating (inserting between) and crosslinking DNA
Natalizumab – Tysabri	Inhibits lymphocyte migration, monoclonal antibody to the integrin α4β1
Alemtuzumab – Lemtrada, CAMPATH	Decreases T, B, and innate immune cells, monoclonal antibody to CD52
Ocrevus, Kesimpta – anti-B cell, that is, anti-CD20	Decreases B lymphocytes, monoclonal antibody to CD20
Nonmyeloablative HSCT – disability-reversing therapy	
Cyclophosphamide/rabbit antithymocyte globulin – Cytoxan/rATG	T- and B-cell lymphopenia followed by reset of adaptive (T and B cell) immunity

DMT, disease modifying therapy; *DNA*, deoxyribonucleic acid; *HTN*, hypertension; *IL*, interleukin; *IFN*, interferon; *MMP*, matrix metalloproteinase; *rATG*, rabbit antithymocyte globulin; *RRMS*, relapsing-remitting multiple sclerosis; *Th*, T helper cell; *UTI*, urinary tract infection; *VLA*, very late antigen.

tumor necrosis factor α, and IFN-γ or Th2 that secretes cytokines IL-4, IL-5, and anti-inflammatory IL-10 (Berger, 2000). GA increases Th2 skewing of T cells (Teitelbaum et al., 1971). In the GALA and other studies, GA decreased the number of relapses but did not alter accumulation of disability (Table 11.2) (Caporro et al., 2014). Side effects of GA (Table 11.3) include injection site reactions, lipoatrophy, skin necrosis, and chest tightness with anxiety (Vartanian et al., 2004).

p0150 Teriflunomide (Aubagio) is a metabolite of leflunomide that is used for rheumatoid arthritis (He et al., 2016). It inhibits the synthesis of pyrimidines that compose two (cytosine and thymine) of the four nucleotides in DNA and two (uracil and cytosine) of the four nucleotides used in ribonucleic acid synthesis. The result is starvation of lymphocyte proliferation and activation. When compared to placebo in the TESMO trial (O'Connor et al., 2011), teriflunomide reduced annual relapse rate. Teriflunomide is secreted by the liver. It undergoes enterohepatic recirculation so that it remains in the circulation for more than 2 years after discontinuing treatment. Due to its long half-life and fetal toxicity, it is essential, even years after stopping treatment, to check serum levels and, if necessary, terminate enterohepatic recirculation with oral activated charcoal or oral cholestyramine before entertaining conception. Due to impairment of pyrimidine synthesis, teriflunomide affects other rapidly dividing cells including hair follicles causing alopecia, gastrointestinal mucosa causing diarrhea and nausea, and skin epithelium precipitating Steven Johnson syndrome or toxic epidermal necrolysis. Other toxicities include headache, hepatic toxicity, and increased infections, especially tuberculosis reactivation.

s0050

Moderately effective disease-modifying therapies: possible short-term disability-slowing therapy

Moderately effective DMTs are taken orally and are of two chemical classes, sphingosine-1-phosphate (S1P) receptor modulators and fumarates. Cladribine is also grouped by some as a moderately effective agent. S1P receptor modulator inhibitors impair T and B lymphocyte egression from lymph nodes (Table 11.2) (Subei and Cohen, 2015). Fingolimod (Gilenya) was the first S1P receptor inhibitor approved for MS. To partially ameliorate some side-effects, selective S1P receptor-modulating drugs, all ending in mod for modulator, were developed and Food

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and Drug Administration (FDA) approved for RRMS including ponesimod (Ponvory), siponimod (Mayzent), and ozanimod (Zeposia). Randomized trials (FREEDOMS (Calabresi et al., 2014b), EXPAND (Cree et al., 2022), OPTIMUM (Kappos et al., 2021), and SUNBEAM (Comi et al., 2019) (Table 11.1)) in RRMS using S1P inhibitors demonstrate a decrease in relapsing and MRI activity but no change in accumulation of disability. Receptors for S1P are located on lymphocytes, smooth muscle endothelial, atrial myocytes, and in the eyes causing side-effects of hypertension (HTN), atrial arrhythmias (bradycardia, atrioventricular block, tachycardia, and atrial fibrillation), and macular edema (swelling of retina with blurred vision) (Subei and Cohen, 2015). Other side-effects include hepatobiliary toxicity, seizure, increased risk of cancer, fetal malformation, and progressive multifocal leukoencephalopathy. Abrupt termination may cause severe rebound MS (Table 11.3).

t0020 ***Table 11.3***

Toxicity of disease-modifying therapy for relapsing-remitting multiple sclerosis.

Drug(s) for disease-modifying therapy for RRMS	Expected major toxicity
Mildly effective DMT – relapse-slowing therapy	
u0040 Interferons (IFN)	Flu like myalgias, aching, headache, ITP, hypo–hyperthyroidism, hepatic toxicity,
u0045 e.g. Betaseron, Avonex, Rebif, Plegridy	leukopenia, injection site reaction, and neutralizing antibodies
Glatiramer acetate i.e. Copaxone	Injection site reaction, lipoatrophy, skin necrosis, chest tightness, and anxiety
Terifluomide – i.e. Aubagio	HA, hair loss, diarrhea, nausea, fetal malformation, tuberculosis, hepatic toxicity, and SJS/TEN
Moderately effective DMT – short-term disability-slowing therapy	
Sphingosine 1 phosphate receptor inhibitor or modulator – e.g. Gilenya, Mayzent, Ponvory, Zeposia	HA, vision loss, macular edema, bradycardia, AV block, tachycardia, hepatic and hepatobiliary toxicity, HTN, seizure, up to 50% increased risk of cancer, fetal malformation, PML, and abrupt termination may cause rebound tumefactive lesions
Fumarates – e.g. Tecfidera, Vumerity	Flushing, abdominal pain, diarrhea, nausea, pancreatitis, hepatotoxicity, lymphopenia, leukopenia, and PML
Daclizumab – i.e. Zinbryta	Autoimmune hepatitis, ITP. Removed from market after postapproval after lethal cases of autoimmune encephalitis
Highly effective DMT – disability-slowing therapy	
Cladribine – i.e. Mavenclad	HA, nausea, alopecia, back pain, infections like URTI, HSV, varicella zoster, tuberculosis, lymphopenia, teratogenesis, and possible increased long-term risk of cancer
Mitoxantrone – i.e. Novantrone	Cardiomyopathy, hepatotoxicity, myelodysplastic syndrome, and leukemia
Natalizumab – i.e. Tysabri	PIRA (underappreciated treatment failure not toxicity per se) PML, herpes infections, respiratory tract infections, fatigue, hypersensitivity reactions, HA, arthalgia, abdominal pain, rebound MS tumefactive flare when stopped
Alemtuzumab – i.e. Lemtrada, CAMPATH	HA, stroke, encephalitis, rash, secondary autoimmune disease, ITP, hypo–hyperthyroidism, anti-GBM disease, systemic lupus erythematosus, antiphospholipid syndrome, and Evans syndrome
Anti-B cell, anti-CD20 – e.g. Ocrevus, Kesimpta	PIRA (underappreciated treatment failure not toxicity per se) nasopharyngitis, URTI, HA, herpes, colitis, hypogammaglobulinemia, neutropenia, thrombocytopenia, increased risk cancer, and PML
Nonmyeloablative HSCT – disability-reversing therapy	
Cyclophosphamide/rabbit antithymocyte globulin – Cytoxan/rATG	Rare bacteremia or UTI when cytopenic, occasional RBC or platelet transfusion, ATG fever (rare with decadron), transient tachycardia, orthostatic hypotension with syncope (may be prevented), drug rash, constipation, nausea (may be prevented), transient hair loss – postdischarge ITP, hypo–hyperthyroidism, age dependent infertility

ATG, antithymocyte globulin; *AV*, atrioventricular; *DMT*, disease-modifying therapy; *HA*, headache; *GBM*, glomerular basement membrane disease; *HSV*, herpes simplex virus; *HTN*, hypertension; *ITP*, idiopathic thrombocytopenic purpura; *MS*, multiple sclerosis; *PIRA*, progression independent of relapse activity; *PML*, progressive multifocal leukoencephalopathy; *RRMS*, relapsing-remitting multiple sclerosis; *TEN*, toxic epidermal necrolysis; *SJS*, Stevens Johnson syndrome; *URTI*, upper respiratory tract infection; *UTI*, urinary tract infection.

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p0160 Fumaric acid esters have anti-inflammatory and antioxidative effects. Dimethyl fumarate has been used to treat psoriasis since the 1950s under the names Fumaderm and Skilarence (Xu et al., 2015; Mrowietz et al., 2018). They induce a mild lymphopenia and shift T cells to a Th2 cytokine profile (Xu et al., 2015). Dimethyl fumarate (Tecfidera) and diroximel fumarate, (Vumerity) are approved for RRMS. In the DEFINE (Gold et al., 2012) and EVOLVE (Wray et al., 2022) trials, they decreased relapse and may slow the rate of
p0190 disability accumulation. Toxicity of fumarates includes flushing, abdominal pain, diarrhea, nausea, hepatotoxicity, lymphopenia, leukopenia, and progressive multifocal leukoencephalopathy. The risk of developing progressive multifocal leukoencephalopathy correlates with level of drug-induced lymphopenia. Dimethyl fumarate and diroximel fumarate decrease annual relapse rate and number of gadolinium-enhancing lesions.

p0165 Daclizumab (Zinbryta) is a monoclonal antibody that binds to CD25, the α subunit of the T cell IL-2 receptor. It was approved after the SELECT randomized trial demonstrated a decrease in both ARR and new MRI activity (Gold et al., 2013). After FDA approval, Zinbryta was removed from the market in 2018 due to 12 cases of autoimmune encephalomyelitis and meningoencephalitis (Liu et al., 2013; European Medicines Agency, 2018; Bianchi and
p0195 Ciccarelli, 2019). Three of twelve (25%) cases were fatal. Toxicity was attributed to an imbalance between suppressive Treg and effector T cells (Liu et al., 2013; European Medicines Agency, 2018; Bianchi and Ciccarelli, 2019). Daclizumab highlights that toxicity is dependent on type of DMT immune-suppressive drug.

p0170 S1P receptor modulators, pyrimidine inhibitors, and fumarates are all oral therapies that decrease ARR, new gadolinium-enhancing lesions, and in some studies brain volume loss, and may reduce short-term disability progression. Moderately
p0200 effective DMTs are relapse-slowing therapies and may be mild short-term disability-slowing therapy when compared to placebo (McGinley et al., 2021).

s0055 Highly effective disease-modifying therapies: disability-slowing therapy

p0175 Highly effective DMTs include the chemotherapy drugs cladribine (Mavenclad) and mitoxantrone (Novantone), and antibodies that carry the suffix – mab for monoclonal antibody: natalizumab, alemtuzumab, ocrelizumab, ofatumumab, and ublituximab. Most highly effective DMTs are infused intravenously except cladribine and ofatumumab that are given orally and subcutaneously, respectively.

p0180 Cladribine is a purine analog that disrupts DNA repair and synthesis (Piro et al., 1994). It was synthesized by chemists at the Scripps Research Institute (La Jolla, CA) and has been approved to treat hairy cell leukemia since 1993 under the name Leustatin (Piro et al., 1994). It causes reduction of T and B lymphocytes. Due to decreased relapse rate, reduced MRI lesions and slowing of disability progression in the CLARITY
p0205 study (Giovannoni et al., 2010), cladribine was approved under the brand name Mavenclad to treat RRMS.

p0185 Although clinically rare, Mavenclad (cladrabine) carries a black box warning of prolonged bone marrow suppression and at high doses may cause irreversible paraparesis or quadriparesis and acute renal failure. Toxicity includes teratogenesis and lymphopenia-related infections like upper respiratory tract infections, herpes simplex virus (HSV), varicella zoster virus (VZV), and tuberculosis. When used to treat leukemia, cladribine causes secondary cancers. When used to treat MS, it has not been shown to increase short-term risk of early cancers (Pakpoor et al., 2015). The risk for increased long-term or late cancer has not been assessed.

Mitoxantrone is an antineoplastic chemotherapy developed in the 1980s as a doxorubicin analog in the hopes of decreasing cardiac toxicity (Faulds et al., 1991). It intercalates between and crosslinks DNA and is a type II topoisomerase inhibitor. Mitoxantrone is an antineoplastic used in regimens to treat leukemia and solid tumors, such as prostate and breast cancer (Faulds et al., 1991). When used as a sole agent for MS, it causes immune suppression via T and B cell lymphopenia. In a placebo-controlled randomized trial (MIMS), mitoxantrone (used under the name Novantrone) decreased clinical relapses and slowed short to midterm disability progression for both RRMS and presumably active-SPMS (Millefiorini et al., 1997; Hartung et al., 2002) but is rarely used nowadays due to other available options and to risk of developing acute myeloid leukemia.

Novantrone carries a black box warning for inducing heart failure and leukemia in patients with MS. The total dose and number of mitoxantrone infusions are limited and cardiac ejection fraction should be checked before each infusion as an early but crude warning sign. Other side-effects of mitoxantrone include bone marrow suppression, febrile neutropenia, infection, nausea, vomiting, abdominal pain, diarrhea, alopecia, headache, dizziness, and rash. Extravasation during intravenous (IV) infusion causes painful skin and muscle necrosis.

Natalizumab (Tysabri) is a monoclonal antibody directed against the adhesion integrin α-4- β-1 (α4β1) (Rice et al., 2005). Blocking α4β 1inhibits T cell extravasation across vascular endothelium. In the AFFIRM (Havrdova et al., 2009) and SENTINEL (Radue et al., 2010) trials, natalizumab decreases relapses and slows disability progression. Natalizumab was removed from the market in 2006 due to deaths from progressive multifocal leukoencephalopathy a viral infection due to John Cunningham virus (JCV) (Kleinschmidt-DeMasters and Tyler, 2005; Ho et al., 2017). It was reintroduced after agreement to enroll all Tysabri patients into the TYSABRI Outreach Unified Commitment to Health database, a restricted prescribing program (Avasarala, 2015). Any patient on Tysabri needs to be closely monitored for JCV indices. Risk of progressive multifocal leukoencephalopathy correlates with duration on Tysabri and rising JCV index. Other toxicities include herpes meningitis, respiratory tract infections, fatigue, hypersensitivity reactions, headache, arthralgia, and abdominal pain. When natalizumab is discontinued, there is a high risk for severe rebound activity within 4–5 months if alternative treatment is not initiated (Fagius et al., 2017).

Alemtuzumab (Lemtrada) is a monoclonal antibody that targets CD52 present in T, B, and innate immune cells (Rao et al., 2012). It was initially named CAMPATH in recognition of Cambridge Pathology at Cambridge University in the United

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Kingdom where it was developed (Warner and Arnason, 2012). The original application was for treatment of chronic lymphocytic leukemia due to persistent lymphocyte depletion (Warner and Arnason, 2012). In the CARE MS 1 (Cohen et al., 2012) and CARE MS II (Coles et al., 2012) trials, Alemtuzumab reduced relapse and accumulation of disability. A significant
p0230 toxicity is ITP (an immune-mediated thrombocytopenia) (Cuker et al., 2020). The CAMMS223 MS study was suspended for 3 months due to three cases of ITP, one of which caused a lethal intracranial bleed from low platelets (Cuker et al., 2020). It was subsequently recommended that platelets be monitored every month for 48 months (Cuker et al., 2020).

p0210 Alemtuzumab may also cause numerous other autoimmune disorders including hypo- or hyperthyroidism in up to 50% of patients, antiglomerular basement membrane disease, systemic lupus erythematosus, antiphospholipid syndrome, and Evans
s0060 syndrome. The cause of B cell autoimmune diseases is persistent and prolonged depletion of CD4 Treg cells that are not available to regulate the rapid rebound and early recovery of naïve B cells (Baker et al., 2017). Another serious complication and FDA warning is ischemic stroke and arterial dissection that may occur during or within days infusion (FDA warning artery dissection stroke, n.d.; Azevedo et al., 2019). The etiology
p0235 remains idiopathic and may or may not be associated with an increase in blood pressure, but patients with a history of HTN should not receive alemtuzumab. Other side-effects include headache, rash, and encephalitis.

p0215 s0065 Ocrelizumab (Ocrevus) and ofatumumab (Kesimpta) are examples of the growing number of available anti-CD20 B cell
p0240 monoclonal antibodies. The history of anti-CD20 antibody therapy for MS began with rituximab when neurologists began to use this patent expired drug off-label for MS (Hauser et al., 2008). Prior to this, MS was viewed as primarily a T cell-driven disease. The encouraging results from early rituximab trials prompted further development that led to trials using anti-CD20 monoclonal antibodies, such as ocrelizumab and ofatumumab.

p0220 In a 2017 randomized controlled trial, ocrelizumab decreased relapses, reduced MRI activity, and slowed accumulation of disability in comparison to IFN-β (Hauser et al., 2017). Ofatumumab, in a 2020 randomized controlled trial, when compared to dimethyl fumarate, decreased relapses, reduced MRI activity, and slowed early disability accumulation (Hauser et al., 2020). Side effects of anti-CD20 monoclonal therapy include hypogammaglobulinemia (sometimes prolonged) with increased risk of infections and rarely cytopenias, such as neutropenia and thrombocytopenia.

p0225 Recent studies show that patients treated with anti-B cell monotherapy may have slow silent accumulation of disability without clinical relapses or MRI changes, a phenomenon termed progression independent of relapse activity (PIRA) (Cree et al., 2019). Relapse-independent accumulation of disability has also been documented for patients on natalizumab (Graf et al., 2021). Recently more specialized MRI analysis documents persistent paramagnetic rim lesions in patients on Ocrevus (Maggi et al., 2023). Such studies suggest that PIRA arises from incomplete treatment of smoldering inflammation not evident by gross clinical relapse or on routine MRI. MRI paramagnetic rim lesions are associated with PIRA and arise from and are consistent with persistent low-grade inflammation, free radical generation, and iron deposition in activated microglia and immune cells located on the periphery of CALs. However, anti-CD20 treatment may partly reduce PIRA (Kappos et al., 2020).

Traditional DMTs are predicated on immune modulation of T cell cytokines (IFN-β, GA, diroximel fumarate), inhibition of T-cell egression and migration (S1P modulators, natalizumab), inhibition of lymphocyte proliferation by either inhibiting nucleoside synthesis (teriflunomide) or disruption of DNA and RNA synthesis (2-CdA, mitoxantrone), or induction of B-cell lymphopenia with monoclonal antibodies against only B cells (ocrelizumab, ofatumumab) or more broadly against T, B, and innate immune cells (alemtuzumab).

DISABILITY REVERSAL THERAPY: DEVELOPMENT OF AUTOLOGOUS CYCLOPHOSPHAMIDE AND RABBIT ANTITHYMOCYTE GLOBULIN NONMYELOABLATIVE PHASE III HSCT RANDOMIZED TRIAL

The multidecades long development (omitting preclinical animal models) leading up to and subsequent results of the phase III randomized MIST trial will be explained herein.

Hematopoietic stem cell transplantation methodology

Due to the source from which HSCs are mobilized, they are termed peripheral blood stem cells (PBSC). Collection of PBSC may occur with administration of cyclophosphamide and granulocyte colony stimulating factor (G-CSF). The most common dose of cyclophosphamide (2.0 g/m^2) used for mobilization is usually infused intravenously over 2 hours. Five days after cyclophosphamide, G-CSF is injected subcutaneously daily for 5 days. Ten days after cyclophosphamide, PBSC are collected by leukapheresis (Fig. 11.2). The PBSC are, depending on regimen, usually cryopreserved without manipulation. In some protocols, PBSC undergo ex vivo selection of CD34$^+$ HSCs to deplete other lymphocytes. Mobilization with cyclophosphamide and G-CSF provides an in vivo purge of lymphocytes, amelioration of disease activity, and prevent a G-CSF-induced flare of MS. An alternative approach is to mobilize PBSC with daily G-CSF and corticosteroids (to prevent disease flare) with leukapheresis on day 4 of G-CSF administration.

When patients are admitted for HSCT, a central line, usually a peripherally inserted central catheter (PICC) antecubital line or a central venous catheter, is placed for venous access. The conditioning regimen is infused via the PICC or central venous catheter over several days. The conditioning regimen may be either nonmyeloablative or myeloablative. After a nonmyeloablative regimen, HSC infusion is not necessary for recovery, but a prudent precaution to shorten neutropenic and thrombocytopenic duration. After a myeloablative regimen, HSCs must be infused as a necessary

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f0015 **Fig. 11.2.** Hematopoietic stem cell transplantation schema on patient going through hematopoietic stem cell collection and hematopoietic stem cell transplantation. (A) Mobilization, 23 hour admission; (B) 10 days later, outpatient apheresis; (C) Approximately 10 days later, admission for 5 days of conditioning (day -5 to -1); (D) Day 0 - stem cell infusion; (E) Remain hospitalized for 8-10 days to receive antibiotics and transfusions; (F) Discharge - usually day 8-10.

s0070 measure to prevent permanent marrow failure (aplasia). After completing the conditioning regimen, PBSCs are thawed and reinfused. Between the day of stem cell infusion (day 0) and engraftment and discharge (usually 6–13 days but duration depends on regimen and center), the patient receives anti-
p0250 biotics, blood product (platelets and RBCs) transfusions, and G-CSF to hasten neutrophil recovery (Fig. 11.2).

Initial multiple sclerosis hematopoietic stem cell transplantation protocol: myeloablative hematopoietic stem cell transplantation for secondary progressive multiple sclerosis

This field was initiated in the United States by hematologists who used total body irradiation (TBI) for leukemias, and as a

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convenient conditioning regimen in preclinical murine models (Burt et al., 1998). For these reasons, initial trials of HSCT for MS in humans used myeloablative cancer regimens including TBI-based regimens (Burt et al., 2003; Nash et al., 2003; Bowen et al., 2012). Murine models indicated that HSCT would not be effective in late SPMS (Burt et al., 1998), yet human HSCT trials began in late SPMS (Burt et al., 2003; Nash et al., 2003; Bowen et al., 2012) for regulatory issues. The reason for this is that novel treatments, because of risks from unforeseen complications, usually begin with treating refractory cases.

The regimen utilized a leukemia myeloablative regimen of cyclophosphamide (120 mg/kg divided 60 mg/kg over 2 days) and TBI (1200 cGy divided 150 cGy bid for 4 days) (Burt et al., 2003). PBSCs were mobilized with cyclophosphamide (2.0 g/m^2) and G-CSF and underwent ex vivo CD34 positive selection to remove lymphocytes (Burt et al., 2003). Twenty patients with SPMS were treated but no patient's neurologic disability (i.e., EDSS) improved. After HSCT, most patients (83% or 10 of 12) with an EDSS score greater or equal to 6.0 continued to neurologically decline (EDSS increased usually by 1.0 or more points in less than 5 years) without new MRI lesions (Burt et al., 2003). Most of the patients with SPMS and an EDSS less than 6.0 also progressed by 0.5 points (Burt et al., 2003). One of the TBI recipients with SPMS (5% or 1 of 20) developed leukemia 5 years after treatment (after initial publication of results) (Burt et al., 2003).

Only 1 patient treated with the TBI/cyclophosphamide regimen had RRMS and that patient was the only patient to demonstrated improvement in neurologic disability (Burt et al., 2003). The EDSS improved (number score decreased) by 2.5 points. To this day more than 22 years later, improvement persists without new evidence of MS and without any MS drugs. While this is anecdotal, such long-term outcomes are not unusual with HSCT (Burt, 2023).

Other centers also started HSCT for MS using a myeloablative leukemia TBI regimen in patients with progressive MS (Nash et al., 2003; Bowen et al., 2012). A regimen of TBI (800 cGy divided 200 cGy BID), cyclophosphamide (120 mg/kg divided 60 mg/kg/day), and equine antithymocyte globulin (eATG) (total 90 mg/kg) was used in 25 patients with progressive MS and one with RRMS (Nash et al., 2003; Bowen et al., 2012).

PBSCs were mobilized with G-CSF and corticosteroids and CD34-selected or purged to remove lymphocytes. In 24 patients with progressive MS, the EDSS worsened in 12 (50%) and improved by 0.5 points in 4 patients (Nash et al., 2003; Bowen et al., 2012). The only patient with RRMS improved by 3.0 EDSS points. One patient died from EBV posttransplant lymphoproliferative disease, and one had significant permanent neurologic worsening related to persistent fever (Bowen et al., 2012). On longer follow up, 3 died from pneumonia, and 1 patient developed myelodysplastic syndrome due to TBI (Bowen et al., 2012). These two TBI-based HSCT trials from different centers failed to improve disability in late SPMS and in most patients, disability worsened despite a very intense myeloablative regimen that due to inclusion of TBI penetrated across the blood–brain barrier. Only 2 patients, one in each trial, demonstrated meaningful improvement in neurologic disability, and both patients had RRMS (Burt et al., 2003; Nash et al., 2003; Bowen et al., 2012).

Intense myeloablative TBI-based regimens were complicated by lethal infections, ATG sustained fever caused neurologic worsening, and TBI caused late myelodysplastic syndrome and leukemia (Burt et al., 2003; Nash et al., 2003; Bowen et al., 2012). TBI-based regimens for MS were abandoned because they were too toxic and without improvement in disability for late SPMS. A safer non-TBI regimen without risk of treatment-induced cancer or significant risk of infections would be necessary to perform HSCT in patients with RRMS.

Nonmyeloablative cyclophosphamide and alemtuzumab phase I trial for relapsing-remitting multiple sclerosis

Recovery from cyclophosphamide-induced cytopenia does not require HSC reinfusion because HSCs are resistant to cyclophosphamide cytotoxicity. Transplant doses (200 mg/kg) of cyclophosphamide (a lymphocyte-specific chemotherapy) as solo therapy without HSC has been used as a successful treatment for aplastic anemia, a hematologic autoimmune disease that causes cytopenia (Brodsky et al., 2010).

Due to encouraging results in patients with severe aplastic anemia (Brodsky et al., 2010), 200 mg/kg of cyclophosphamide without HSCs was used as solo therapy to treat MS (Gladstone et al., 2006; Harrison, 2012). Unlike traditional DMTs, transplant doses of cyclophosphamide significantly reversed neurologic disability in patients with RRMS without further DMTs (Gladstone et al., 2006; Brodsky et al., 2010). However, most patients relapsed by 3 years either without a posttransplant DMTs or with addition of posttransplant maintenance GA (Gladstone et al., 2006).

To minimize the incidence of relapse, in the first nonmyeloablative HSCT protocol for RRMS, alemtuzumab (20 mg) was added to cyclophosphamide given at a total dose of 250 mg/kg divided 50 mg/kg (2.0 g/m^2) for mobilization of PBSC and 200 mg/kg during HSCT (Burt et al., 2009). PBSCs were reinfused to hasten recovery from cyclophosphamide-induced cytopenia. Using this regimen, significant improvement (> 1 point) in neurologic disability (EDSS score) occurred in 81% of patients with no further post treatment DMTs (Burt et al., 2009). By 3 years after HSCT 76% remained treatment free without evidence of relapse or disease activity (Burt et al., 2009). The regimen of cyclophosphamide and alemtuzumab was well tolerated without fever or serious infections but 17% developed late ITP at 6 months to 3 years after transplant (one case occurred after publication) (Burt et al., 2009). As mentioned earlier, monotherapy with alemtuzumab causes B cell-mediated autoimmune diseases including ITP due to rapid recovery of immature B cells but delayed recovery of T cells that regulate B cells (Baker et al., 2017). Furthermore, two patients treated with cyclophosphamide and alemtuzumab developed cancer; one had breast in situ ductal carcinoma 3 years posttransplant and the other (who had also received pre-

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HSCT mitoxantrone) developed lymphoma 5 years posttransplant (Burt et al., 2009). The high late incidence of posttransplant B-cell dysregulation and ITP and concern about late solid tumors prevented moving this regimen forward to a phase II or III trial.

p0315 s0080

Nonmyeloablative cyclophosphamide and antithymocyte globulin phase II regimen for relapsing-remitting multiple sclerosis

p0295 Due to the risk of ITP, alemtuzumab was replaced with rabbit ATG (rATG) (6.0 mg/kg) (Burt et al., 2015). The total dose of cyclophosphamide (250 mg/kg divided as 50 mg/kg for mobilization and 200 mg/kg for the conditioning regimen) was unchanged (Burt et al., 2015). PBSCs were not manipulated (unselected). The cyclophosphamide and rATG conditioning regimen was a phase II study of 118 patients with RRMS treated on study, 27 SPMS patients were treated on a compassionate basis off study (Burt et al., 2015). All patients at enrollment had an EDSS between 2.0 and 6.0.

p0300 All patients on study had failed at least two prior DMTs and during the preceding year had either at least two clinical relapses treated with corticosteroids, or one clinical relapse treated with a corticosteroid and at a separate time a gadolinium-enhanced lesion on MRI (MRI imagining equivalent to a clinical relapse). The only positive cultures during HSCT admission were one blood culture positive for coagulase-negative staphylococcus and four stool cultures positive for *Clostridium difficile*. Four patients (3.1%) developed late ITP within 2 years of HSCT. No patient treated with cyclophosphamide and rATG developed a cancer on follow-

p0320 up. There was no treatment-related mortality (Burt et al., 2015). After HSCT, the median RRMS disability score improved from a pretransplant score of 4.0 to 3.0 at 1-year posttransplant and to 2.5 from 3 to 5 years after HSCT. Treatment-free, relapse-free survival (RFS) was 89% at 2 years and 80% at 4 years (Burt et al., 2015).

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Randomized cyclophosphamide and rabbit antithymocyte globulin phase III multiple sclerosis

s0090 **immune suppression versus transplant trial: trial design**

p0305 The nonmyeloablative cyclophosphamide and rATG phase II trial (Burt et al., 2015) justified using this regimen as a randomized

p0325 phase III trial for RRMS (Burt et al., 2015). The randomized trial was given the acronym MS immune suppression versus transplant (MIST) trial (Burt et al., 2019). MIST was run at four university centers in four countries: the United States, Sweden, the United Kingdom, and Brazil (Burt et al., 2019).

p0310 Almost all prior DMT trials had compared the pharmaceu-

p0330 tical drug (DMT) to a placebo or to the weakest DMT available, that is, an IFN or GA. The comparator arm for MIST was the best available DMT as determined by the treating neurologist. Sixty percent of the patients on the control arm were randomized to natalizumab (Burt et al., 2019). If you were already failing (having acute attacks) on natalizumab, the patient was randomized to a different class of DMT, such as fingolimod. The neurologist on the control arm was allowed to change the DMT during the trial as clinically indicated by toxicity or new acute attacks. On the treatment arm, after HSCT, all DMTs and immune-based therapies were discontinued unless or until occurrence of a confirmed relapse.

In the MIST trial, disability worsening was the primary endpoint. Disability worsening was defined as an increase in EDSS by 1.0 or more points sustained for at least 6 months (Burt et al., 2019). After being treated with a DMT for at least 1 year, patients on the DMT control arm who met the primary endpoint of sustained increase in disability were allowed to cross over to HSCT. By allowing crossover, the control arm functioned as its own control. Allowing a crossover after 1 year on study prevented long-term comparison between the two treatment arms. Crossover was allowed to achieve trial equipoise. In other words, the two treatment arms must have relatively equal efficacy because it would be unethical to give a highly effective treatment to one group but not another. On the group level, DMTs do not improve neurologic disability. In prior high-dose cyclophosphamide studies (Gladstone et al., 2006; Harrison, 2012) and in the phase II nonmyeloablative cyclophosphamide-based regimen (Burt et al., 2015), neurologic disability improved. From existing data, the two arms would be unequal in the primary outcome, so after 1 year, a crossover was allowed. Based on the phase II trial using the same regimen (Burt et al., 2019), it was accurately predicted a priori that 110 patients, 55 in each arm would be sufficient to demonstrate a statistically significant difference in the primary outcome (Burt et al., 2019).

Ideally, randomized trials should be double blinded with neither the physician nor patient knowing treatment. For HSCT it is impossible to blind the patient as the transplant arm requires a 2-week hospitalization and will have obvious expected side-effects like transient alopecia and blood product transfusions. However, the evaluating neurologists at each site were blinded to treatment course.

Randomized cyclophosphamide and rabbit antithymocyte globulin multiple sclerosis immune suppression versus transplant (MIST) trial – minimizing transplant regimen toxicity

Toxicity depends on the drugs in the regimen, drug doses, and mitigation strategies. Despite the importance of such practices to minimize toxicity, mitigation strategies are not universal and vary in degree and method by center. The toxicities and mitigation strategies for the MIST trial cyclophosphamide/rATG regimen will be explained (Burt et al., 2015, 2019).

Rabbit ATG (Thymoglobulin) was infused over 10 hours at 0.5 mg/kg on day –5, 1.0 mg/kg on day –4, and 1.5 mg/kg on days –3, –2, and –1 for a total dose of 6.0 mg/kg (Burt et al., 2019). To minimize ATG-related first pass fever, ATG is dose escalated over days –5, –4, and –3. To further reduce the incidence of ATG fever, a corticosteroid, such as solumedrol at

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p0350 1000 mg is infused before each dose of ATG. While effective at that dose in preventing fever on ATG infusion day, due to a relatively short half-life (12–18 hours), late ATG fever will often develop on day 0, 1, or 2 after completing the last dose of ATG infusion on day –1. An oral prednisone taper of 60 mg for 3 days (days 0, 1, and 2), 40 mg for 2 days (days 3 and 4), and 20 mg PO for 2 days (days 5 and 6) will decrease but not eliminate the risk of late ATG fever.

p0335 Substitution of methylprednisolone with dexamethasone (48.5 mg IV) given before each dose of ATG also minimizes the incidence of infusion-related ATG fever and due to its longer half-life (36–54 hours) prevents the risk of late ATG fever. If despite corticosteroids, acute ATG-related fever occurs, etanercept (Enbrel at 25 mcg sq) injected once is usually sufficient to stop ATG-induced fever. The importance of preventing ATG-related fever is to avoid confusion with and workup for infection. Fever even without infection causes a pseudo flare of MS (Uhthoff phenomenon) (Jain et al., 2020) with acute neurologic worsening that will also lead to workup for active MS including an unnecessary MRI. While controversial, sustained and persistent high fever may lead to a late sustained increase in EDSS (Burt et al., 2015). High-dose corticosteroids used to prevent ATG fever may cause transient insomnia, mania, or psychosis. Psychosis usually begins as insomnia and pressured speech and when detected may be prevented or reversed with low dose olanzapine given at bedtime. If this is not recognized, a full-blown psychotic episode may require restraints and will be difficult to manage during neutropenia.

s0095

p0355

p0340 Cyclophosphamide is infused over 2 hours at 50 mg/kg/day on days –5, –4, –3, and –2 for a total dose of 200 mg/kg (Fig. 11.3).

p0360 For people who are more than 25% above ideal weight, cyclophosphamide is given at ideal weight plus 40% of difference between actual and ideal weight. Cyclophosphamide is dose-capped at 4 g/day (transplant dose capped at 16 g). In this regimen, to minimize cardiac toxicity, the combined mobilization and transplant cyclophosphamide dosage should not exceed 250 mg/kg to minimize cardiotoxicity with arrhythmias and a transient but potentially lethal drop in ejection fraction and heart failure (Goldberg et al., 1986). To further minimize cardiotoxicity, there should be a minimum of 18–21 days between the mobilization dose (2 g/m^2 is equivalent to 50 mg/kg) and starting the transplant dose (200 mg/kg) of cyclophosphamide.

p0345 p0365 Because cyclophosphamide is emetogenic, the first dose is premedicated with aprepitant. Every cyclophosphamide dose is premedicated with ondansetron and lorazepam. Breakthrough nausea is treated with prochlorperazine, lorazepam, or small doses (4 mg) of ondansetron. For refractory nausea, low-dose oral olanzapine is effective. A common side-effect of ondansetron is constipation that if uncorrected may cause abdominal bloating and pain. This can be prevented with a daily stool softener, such as docusate sodium, monitoring bowel movements, and if constipated a prophylactic laxative, such as lactulose and if no relief, oral magnesium citrate.

To prevent bladder toxicity (hemorrhagic cystitis), normal saline hydration at approximately 100 cc/h with furosemide diuresis (40 mg IV bid) is started before the first and continued until 12 hours after the last cyclophosphamide dose. To avoid volume overload, furosemide and hydration are adjusted by monitoring liquid intake and output and daily weights. Bolus furosemide may rarely lead to swift excessive diuresis with flank pain akin to nephrolithiasis. This is managed by switching back to oral furosemide diuresis.

Randomized cyclophosphamide and rabbit antithymocyte globulin multiple sclerosis immune suppression versus transplant trial – transplant infections, secondary autoimmune diseases, and cancer

To minimize risk of JCV-induced progressive multifocal leukoencephalopathy, patients undergo a drug washout interval before HSCT (4–5 months for natalizumab and ocrelizumab, and 2–3 months for ofatumumab, fingolimod, and dimethyl fumarate). Prior teriflunomide treatment requires clearance with oral cholestyramine or activated charcoal. IFN and GA are continued until mobilization. Prior mitoxantrone and alemtuzumab are generally considered contraindications for HSCT. Mitoxantrone due to its inherent high risk of late myelodysplastic syndrome and heart failure. Prior alemtuzumab due to persistent long-term CD4 T-cell lymphopenia. Broad spectrum antibiotic coverage is started on day 0. Antibiotic coverage during neutropenia is important since steroids will mask fever and many patients especially those on prior anti-CD20 B-cell therapy are hypogammaglobulinemic and functionally asplenic.

Depending on local protocol, patients usually remain on oral valacyclovir for one year and oral daily fluconazole and oral three times a week (TIW) trimethoprim-sulfamethoxazole for 90 days after HSCT. Serum CMV is monitored by PCR weekly for 1 month and then every 2 weeks for 2 months. If PCR positive, acyclovir is switched to oral valganciclovir (900 mg twice daily) until seronegative. Due to the recent COVID pandemic and common use of anti-CD20 B-cell DMTs, many patients have profound hypogammaglobinemia. To avoid post-discharge COVID, other viral infections, and mucosal surface (e.g., URTI) bacterial infections, IV immunoglobulin is infused once (400 mg/kg) on day +8.

Using this regimen, inpatient bacteremia or viral or fungal infections are uncommon. During HSCT in the randomized trial, there was one case of *C. difficile* diarrhea and one case of *Escherichia coli* urinary tract infection (UTI). After HSCT, all DMTs and immune-suppressive or modulating drugs are discontinued while patients on DMTs continue indefinitely on immune-suppressive DMTs. Not surprisingly, after discharge, there were more late infections in the DMT group with 0.23 infections per patient per year versus 0.19 in the HSCT group. Infections in both groups were most common on mucosal surfaces: sinusitis, pharyngitis, otitis media, URTI, UTIs, and *C. difficile* diarrhea. Late viral infections in both groups were

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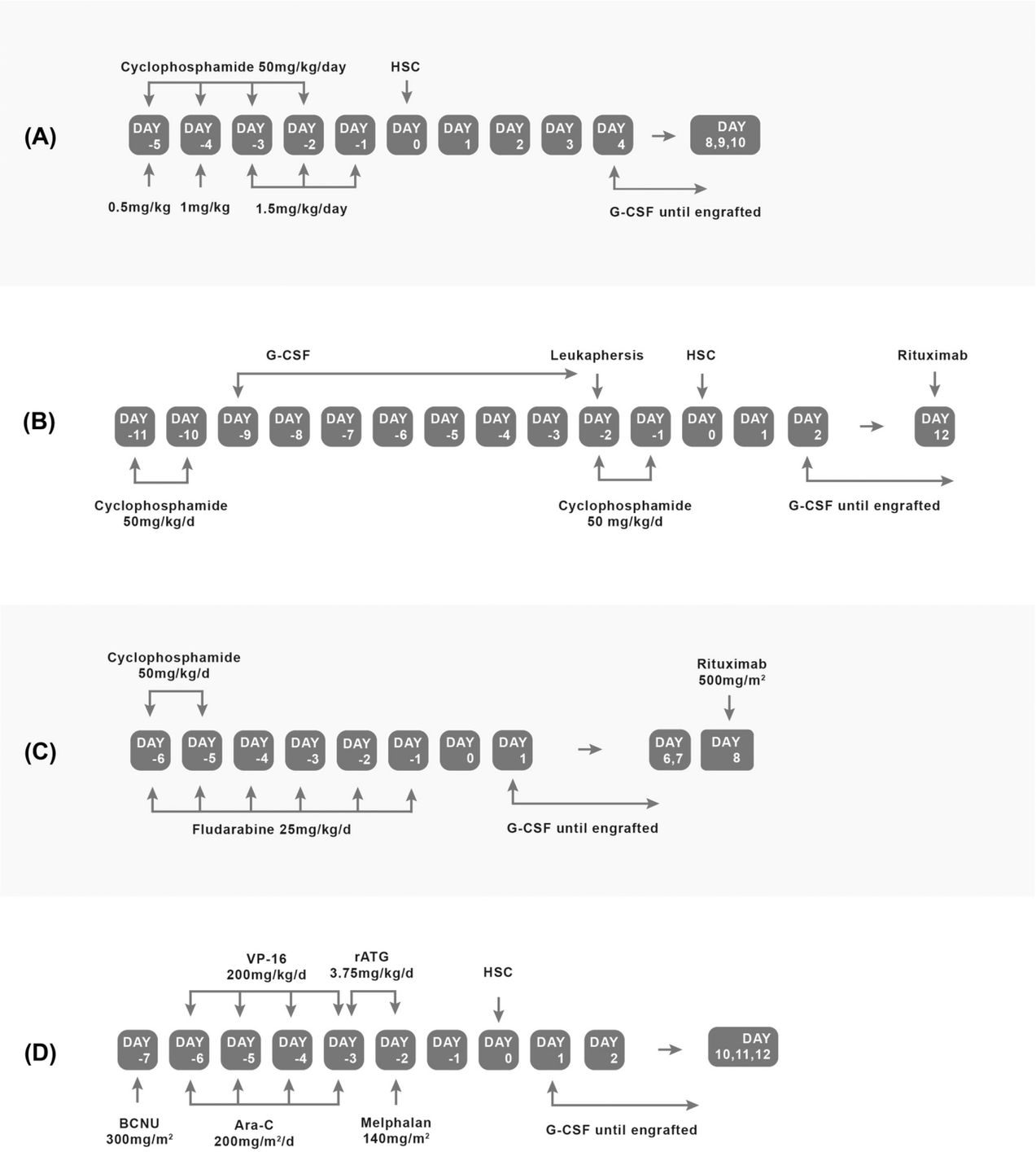

f0020 **Fig. 11.3.** Common conditioning regimens currently in use to treat multiple sclerosis. (A) Cyclophosphamide 50 mg/kg/day from day -5 to day -2, HSC on day 0, G-CSF until engrafted from day 1 to day 4 and day 8, 9, 10. Dosages: 0.5 mg/kg on day -5, 1 mg/kg on day -4, 1.5 mg/kg/day from day -3 to day -2; (B) Cyclophosphamide 50 mg/kg/day from day -11 to day -3, G-CSF from day -10 to day -1, leukapheresis on day -2, HSC on day 0, G-CSF until engrafted from day 1 to day 2 and Rituximab on day 12; (C) Cyclophosphamide 50 mg/kg/day from day -6 to day -2, Fludarabine 25 mg/kg/day from day -6 to day -2, HSC on day 0, G-CSF until engrafted from day 1 to day 2 and Rituximab 500 mg/m² on day 8; (D) BCNU 300 mg/m² on day -7, Ara-C 200 mg/m²/day from day -6 to day -5, VP-16 200 mg/kg/day from day -4 to day -3, rATG 3.75 mg/kg/day from day -3 to day -2, Melphalan 140 mg/m² on day -2, HSC on day 0, G-CSF until engrafted from day 1 to day 2 and day 10, 11, 12.

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s0110 VZV dermatomal infection and seasonal outpatient influenza. In the HSCT group, VZV infections were more common and occurred after stopping prophylactic acyclovir at 1 year. Despite an often-high JCV index, no patient developed progressive p0390 multifocal leukoencephalopathy. Using this non-myeloabaltive regimen that limited total ATG to 6.0 mg/kg no patient developed or was treated to prevent a symptomatic EBV infection.

p0370 ITP occurred in one HSCT patient and another case of ITP was attributed to fingolimod that recurred when fingolimod was restarted. Three cases of hyperthyroidism and one episode of hypothyroidism occurred after HSCT. No cancers or deaths occurred in either arm.

p0395

s0100

Randomized cyclophosphamide and rabbit antithymocyte globulin multiple sclerosis immune suppression versus transplant trial: neurologic outcome

p0375 One year after HSCT, mean EDSS scores decreased (improved) from 3.38 to 2.36 but increased (worsened) from 3.31 to 3.98 in the DMT group ($p < 0.001$) (Burt et al., 2015). Disease volume on MRI significantly decreased in the HSCT group but increased in the DMT group (Burt et al., 2019). In the HSCT group, Short Form 36 (SF-36), QOL improved from 51 at baseline to 70 at 1 year, whereas in the DMT group, QOL worsened from 50 at baseline to 46 at 1 year ($p < 0.001$) (Burt et al., 2019). After 1 year, most patients on the DMT arm p0400 crossed over to HSCT. Median time to disability progression was 24 months in the DMT group but could not be calculated in the HSCT group because of too few events ($p < 0.001$). NEDA defined as no relapses, no progression, and no new or increasing T2 lesion on MRI was significantly different between the two groups ($p > 0.001$). NEDA in the HSCT group was 98% at 1 year, 93% at 2 years, 90% at 3 years, and 78% at 5 years. In the DMT group, NEDA was 21% at 1 year, 12% at 2 years, 6% at 3 years, and 3% at 5 years (Burt et al., 2019).

p0380 EDSS, QOL, and NEDA-3 outcomes from nonmyeloablative HSCT are markedly superior compared to reports from highly effective DMTs trials (Fig. 11.4) (Burt et al., 2020). When all 507 patients both on and off study treated with a cyclophosphamide ATG regimen were reported, mortality was 0.4% p0405 arising from one sickle crisis before HSCT and one legionella pneumonia during HSCT acquired from contamination of the hospital water supply (Burt et al., 2022). For the entire group of 507 patients, EDSS improved by > 1.0 points in RRMS, by 0.5 points in active SPMS (defined as SPMS with a new MRI lesion in the prior year) but not in patients with nonactive SPMS (no new MRI activity in the prior year) (Burt et al., 2022).

s0105

Other nonmyeloablative regimens

p0385 Other common nonmyeloablative (and myeloablative) regimens in current use to treat multiple sclerosis are shown in Figures 11.3 and 11.5.

Cyclophosphamide cumulative dose 300 mg/kg and rabbit antithymocyte globulin total dose 7.5 mg/kg – high cardiac toxicity and EBV infection

A London consortium of transplant centers reported a cases series of HSCT in 120 patients with different types of MS (Nicholas et al., 2021). The majority (52%) had progressive MS (either PPMS or SPMS) while 48% had RRMS. Two different mobilizing regimens to collect PBSCs were utilized: cyclophosphamide 4 g/m^2 in 62 patients and cyclophosphamide 2 g/m^2 in 52 patients. The PBSC were unmanipulated. The conditioning regimen was cyclophosphamide 200 mg/kg with two different doses of ATG of either 7.5 mg/kg (2.5 mg/kg/day) in 72 patients or 6.0 mg/kg (2.0 mg/kg/day) in 48 patients (Nicholas et al., 2021).

There were three treatment-related deaths (2.5%) that were related to cardiac failure with resultant pulmonary edema and volume overload. The etiology of heart failure is not clarified but may have been secondary to a combination of cyclophosphamide dosing and ATG-related fever (Jain et al., 2020). Mobilization with 4.0 g/m^2 which is equivalent to 100 mg/kg when combined with a conditioning regimen of 200 mg/kg yields a total cyclophosphamide dose of 300 mg kg. Clinically evident cardiotoxicity occurs above a total acute dose of 250 mg/kg. Based on large center experience, significant cardiac complications can be mitigated using weight-adjusted cyclophosphamide doses, capping of total cyclophosphamide dose, building in a minimum time interval between mobilization and transplant cyclophosphamide exposure in addition to prompt management of ATG-related fever, and strict attention to fluid and electrolyte balance.

EBV reactivation was significantly higher at the center dosing ATG at 7.5 mg/kg (Nicholas et al., 2021). Twenty patients required treatment with rituximab for EBV reactivation to prevent EBV-related fever and PLTD. Symptomatic EBV to this extent has not been reported when using cyclophosphamide (200 mg) and ATG at 6.0 mg/kg. Patients with systemic sclerosis (SSc, scleroderma) treated with 200 mg/kg cyclophosphamide and ATG at 7.5 mg/kg have died from EBV-related posttransplant lymphoproliferative disease (van Laar et al., 2014). Following HSCT for both MS (Nicholas et al., 2021) and SSc (van Laar et al., 2014), symptomatic reactivation of EBV appears to be related to the high dosage of ATG (7.5 mg/kg divided 2.5 mg/kg/day) in those regimens.

Fever from ATG or symptomatic EBV reactivation can lead to significant temporary or permanent worsening of neurologic disability. Higher fever occurred at an ATG dose 7.5 mg/kg compared to 6.0 mg/kg. Fever is not seen to this extent in programs that cap rATG at 6.0 mg/kg, minimize first pass fever by starting at 0.5 mg/kg, use appropriate corticosteroid prophylaxis, and when required etanercept treatment. It is not just the regimen used, but the cumulative drug doses employed in the regimen and standard of care to mitigate drug complications that influence toxicity. Strategies to mitigate cyclophosphamide heart failure and prevent fever from pyrogens, such as ATG are important in preventing toxicity and improving outcomes.

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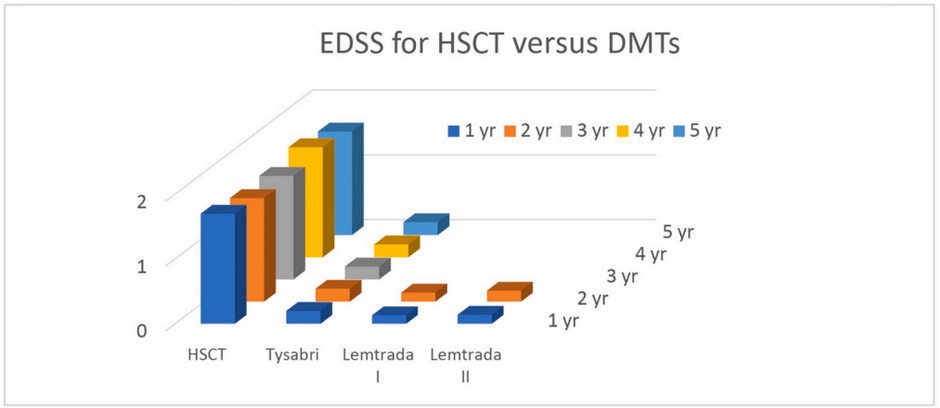

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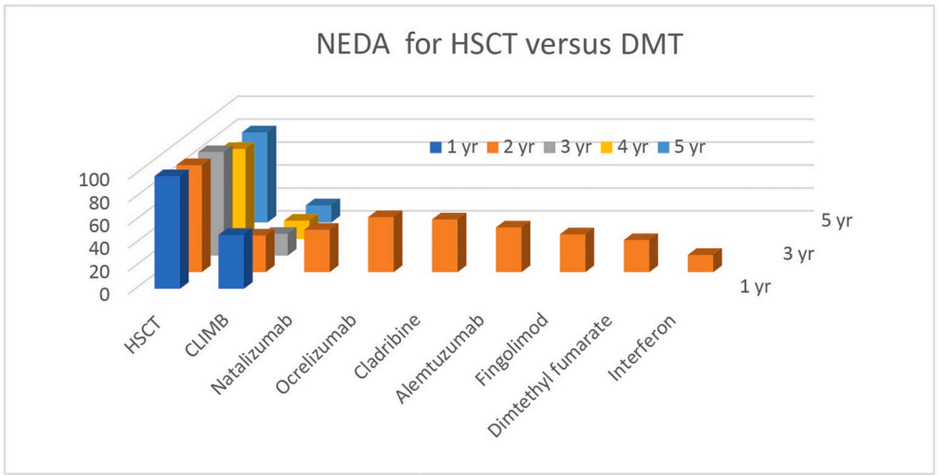

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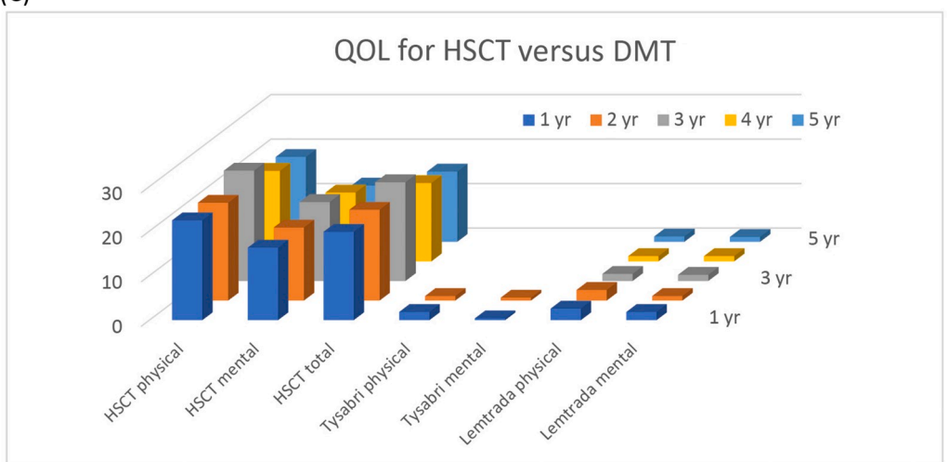

f0025 **Fig. 11.4.** (A) Expanded disability status scale (EDSS); (B) No evidence of disease activity (NEDA-3) and (C) Quality of life (QOL) and after nonmyeloablative hematopoietic stem cell transplantation (HSCT) versus highly effective disease-modifying therapy (DMT) trials.

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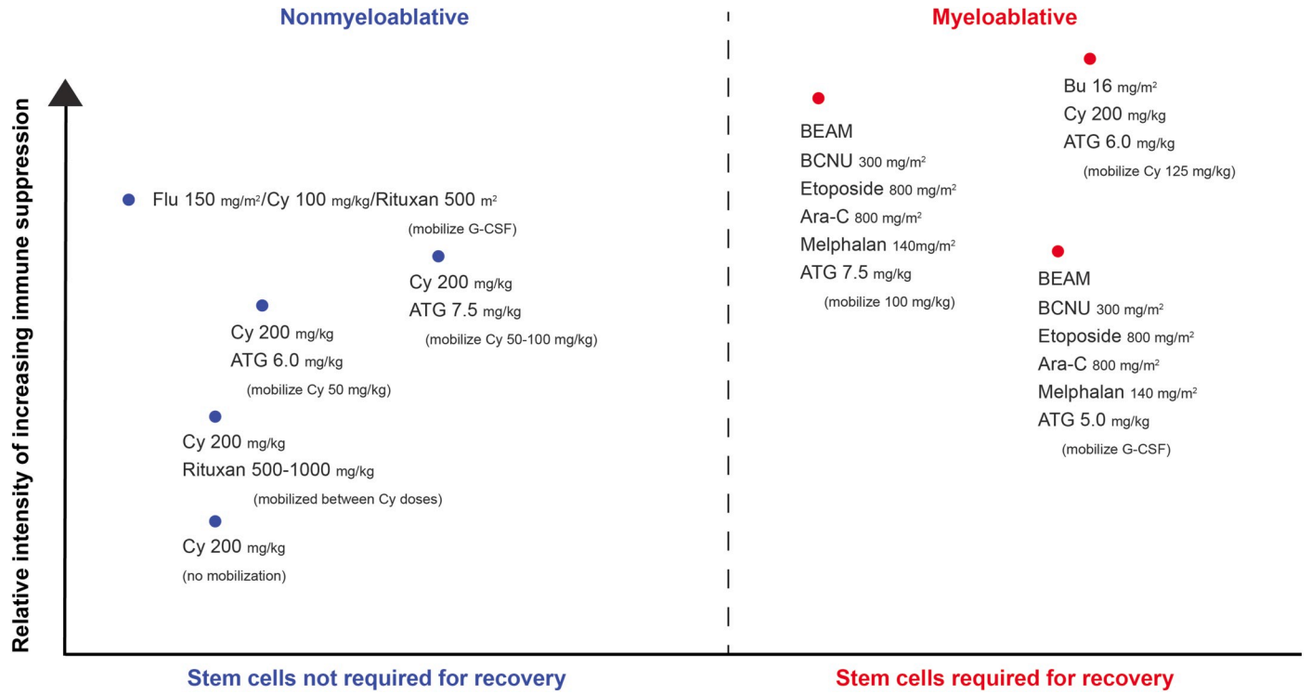

f0030 **Fig. 11.5.** Relative immune-suppressive intensity of different regimens currently used for multiple sclerosis.

s0115 ## Cyclophosphamide rituximab regimen – splitting dose of cyclophosphamide to decrease cardiac toxicity and electrolyte abnormalities

p0410 Two centers under one study umbrella with a large collective experience decrease potential cyclophosphamide cardiotoxicity by splitting the 200 mg/kg dose into two doses of 100 mg/kg (50 mg/kg on days –11 and –10) with the second 100 mg/kg dose also divided into 50 mg/kg/day on days –2 and –1. Each 100 mg/kg cyclophosphamide dose is separated by seven consecutive cyclophosphamide-free days (Murrieta-Álvarez et al., 2021; Olivares-Gazca et al., 2022). The first two doses of cyclophosphamide (100 mg/kg) act both as immunosuppressors and stem cell mobilizers used to collect stem cells on day-2 before starting the second 100 mg dose of cyclophosphamide (Fig. 11.3). PBSCs are neither manipulated nor cryopreserved but are kept in conventional blood bank incubator for 48 hours until reinfused on day 0. Cyclophosphamide is given by actual weight for a total dose of 200 mg/kg. Rituximab which is not generally pyrogenic is given once at 1000 mg on day 12.

p0415 The transplants are done as an outpatient, and in 1000 transplants, mortality occurred in 2 patients (0.2%) due to gram negative bacteremia in patients with comorbidities (Murrieta-Álvarez et al., 2021; Olivares-Gazca et al., 2022). Prophylactic oral bactrim, itraconazole, and acyclovir were started on day –10. Broad-spectrum IV antibiotics were not administered during afebrile neutropenia. Outcomes in disability were limited to self-reporting, and the regimen has not been tested in a randomized trial which are current weaknesses (Bowen et al., 2001; Collins et al., 2016; Ruiz-Argüelles et al., 2019). The self-reported 2-year NEDA-2 (no relapses, no progression) was 80% (Murrieta-Álvarez et al., 2021; Olivares-Gazca et al., 2022).

Fludarabine 150 mg/m^2 + cyclophosphamide 100 mg/kg + Rituximab 500 mg/m^2 decreases duration of neutropenia and transfusion requirements

An experienced large single center sequentially developed different low-intensity regimens in an attempt to optimize transplant safety (Melnichenko et al., 2022; Rukavitcyn et al., 2022). In all regimens, PBSCs are mobilized without cyclophosphamide by using only daily G-CSF (10 μg/kg/day) with apheresis on day 5 (after 4 days of G-CSF 10 μg/kg and Solumedrol 500 mg/day – 5 days). They reported a similar RFS between a myeloablative-reduced intensity BEAM-like lymphoma regimen and a nonmyeloablative regimen of rituximab (500 mg/m^2) and cyclophosphamide dosed at 200 mg/kg by adjusted weight (when actual weight is > 25% ideal weight, dose at ideal weight plus 40% difference between actual and ideal weight) (Melnichenko et al., 2022; Rukavitcyn et al., 2022). The total dose of cyclophosphamide was not capped until 20 total grams or 5 g/day.

In the most recent iteration, the conditioning regimen is made up of fludarabine (150 mg/m^2), cyclophosphamide (100 mg/kg), and rituximab (500 mg/m^2). With these changes, the duration of neutropenia has decreased from 9.6 to 6.3 days (Rukavitcyn et al., 2022). Patients requiring platelet transfusions decreased from 63% in their prior nonmyeloablative

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regimen to only 12% (Rukavitcyn et al., 2022). Similar decreases in duration of neutropenia and transfusion requirements occurred when patients with SSc were treated with a similar fludarabine-based regimen (Burt et al., 2021). The long-term neurologic outcome, secondary autoimmune disorders, and a randomized trial that are blinded to the evaluating neurologist is indispensable for confirmation.

Summary on reducing nonmyeloablative toxicity

Nonmyeloablative regimens were developed because the intensity and toxicity of myeloablative regimens were perceived as less favorable in terms of risk benefit for patients with RRMS. The experiences from current nonmyeloablative regimens for MS emphasize the importance of capping cyclophosphamide daily and total dose, dosing by adjusted body weight, excluding patients with low cardiac ejection fractions or significant cardiac history, and having a minimum interval between mobilization and transplant doses of cyclophosphamide and mitigation strategies for ATG fever.

Although the risk of antibiotic resistance is always a concern, to date during HSCT for MS no drug-resistant organisms have developed during the regimen-induced one-time short period of neutropenia. On the other hand, deaths from bacteremia have occurred in centers not implementing broad antibiotic prophylaxis or broadening antibiotic coverage for culture-negative persistent fever. Studies confined to this group of patients treated during the one-time regimen-induced neutropenic interval that correlates development of antibiotic resistance and infectious mortality versus prophylactic antibiotic usage are lacking. To date, in large-volume experienced centers using a nonmyeloablative regimen, the death rate ranges from 0% to 0.8% (Burt et al., 2009, 2015; Murrieta-Álvarez et al., 2021; Burt et al., 2022; Melnichenko et al., 2022; Rukavitcyn et al., 2022; Silfverberg et al., 2024a).

MYELOABLATIVE IMMUNE CONDITIONING REGIMEN

Myeloablative cancer regimens were the first regimens used for HSCT of MS (Fassas et al., 1997; Burt et al., 1998; Nash et al., 2003; Bowen et al., 2012) and were first applied to progressive forms of MS (predominately SPMS), that is, the TBI containing myeloablative regimens discussed earlier. One of the most potent non-TBI myeloablative regimen that was designed to eliminate MS activity uses a myeloablative leukemia regimen composed of busulfan, cyclophosphamide, and ATG used in Canada (Atkins et al., 2016) (Fig. 11.5). Due to toxicity concerns, the application of myeloablative HSCT for MS has coalesced around a less intense myeloablative regimen of BEAM and ATG that was originally developed for and is still used as a transplant regimen for lymphomas. BEAM plus ATG developed by Fassas in Thessaloniki, Greece was the first transplant regimen used to treat MS (in a cohort with SPMS) (Fassas et al., 1997).

In older patients with SPMS, high disability scores, and a T cell-depleted PBSC graft, BEAM and ATG had an initial transplant-related mortality risk of approximately 5% (Fassas and Kimiskidis, 2003). Due to strong suppression of subsequent MRI activity and perceived stabilization of neurologic disability, a small randomized European trial was performed to compare HSCT to mitoxantrone which at that time was considered the best available DMT (Mancardi et al., 2015).

Although requiring a common increase in EDSS by at least 1.0 point and one or more gadolinium-enhancing lesions within the prior 12 months, a heterogeneous group of 21 patients were enrolled: RRMS (33%), SPMS without relapses (29%), SPMS with relapse (33%), and relapsing progressive MS (5%) (Mancardi et al., 2015). Patients were randomized between BEAM/ATG (9 patients) versus mitoxantrone 20 mg q month × 6 months (12 patients). PBSC were mobilized with 4 g/m^2 cyclophosphamide and cryopreserved without manipulation. The regimen consisted of BEAM composed of BCNU 300 mg/m^2 at day −7; cytosine-arabinoside, 200 mg/m^2; etoposide, 200 mg/m^2 from day −5 to day −2; and melphalan 140 mg/m^2 at day −2 plus ATG 7.5 mg/kg divided 3.75 mg/kg/day at day 11 and 12 (Mancardi et al., 2015).

Transplants were complicated by ATG-related fever (febrile neutropenia) and BEAM-related mucositis and diarrhea. Significant adverse events were restricted to the BEAM/ATG treatment arm and included bacterial sepsis, systemic candidiasis, life-threatening engraftment failure, and life-threatening ATG-related fever, dyspnea, and hypoxemia (Mancardi et al., 2015).

All patients were followed for at least 4 years after HSCT. Compared to mitoxantrone, HSCT significantly reduced the number of relapses ($p = 0.026$) and number of new MRI lesions ($p < 0.001$) (Mancardi et al., 2015). There was no difference in mean disability progression. Failure of EDSS to improve may have been due to the small number of patients and heterogeneity of patients (mostly progressive MS) and the few patients with RRMS being mostly randomized to mitoxantrone (Vasselli, 2015).

An American trial enrolled 25 patients with RRMS in a nonrandomized phase 1 BEAM plus ATG trial (Nash et al., 2015). PBSCs were mobilized with G-CSF and CD34 selected before cryopreservation. Prednisone was taken to prevent a G-CSF-related MS flare, although one G-CSF-induced flare occurred in a prednisone-noncompliant patient (Nash et al., 2015). BEAM was given at standard doses and rabbit ATG at 5.0 mg/kg divided 2.5 mg/kg/day on days −2 and −1. Gastrointestinal toxicity and mucositis were common. Fever, although present, was not documented as a separate toxicity and was not evaluated for transient or late effect on EDSS. Twelve (48%) patients had bacterial infections (not further identified). Two late deaths occurred, one from suicide and one from asthma (Nash et al., 2015). In evaluable patients, for up to 5 years after HSCT, the EDDS improved (decreased) by a median of 0.5 from baseline (Nash et al., 2015). After 5 years, 3 of 24 patients relapsed. Progression-free survival (PFS), clinical RFS, and MRI activity-free survival were 91.3%, 86.9%, and 86.3%, respectively (Nash et al., 2017).

In a registry-based study of 210 patients treated with BEAM/ATG, 122 had RRMS and 88 had progressive MS (predominately SPMS, not subtyped as active-SPMS or nonactive SPMS) (Boffa et al., 2021). Conditioning regimens and dosages used (and number of patients) included: BEAM and ATG (158 patients), BEAM (10 patients), FEAM (F for fotemustine) (4 patients),

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p0485 cyclophosphamide at 200 mg/kg and ATG (10 patients), cyclophosphamide at 120 mg/kg and ATG (Rubertone and Brundage, 2002), thiotepa and cyclophosphamide (10 patients) and others (2 patients). Three patients or 1.4% died (causes not given). Regimen-related toxicities were not summarized. For RRMS, PFS was 85.5% and 71.3% at 5 and 10 years, respectively. In patients with progressive MS, PFS was 71.0% and 57.2% at 5 and 10 years, respectively (Boffa et al., 2021).

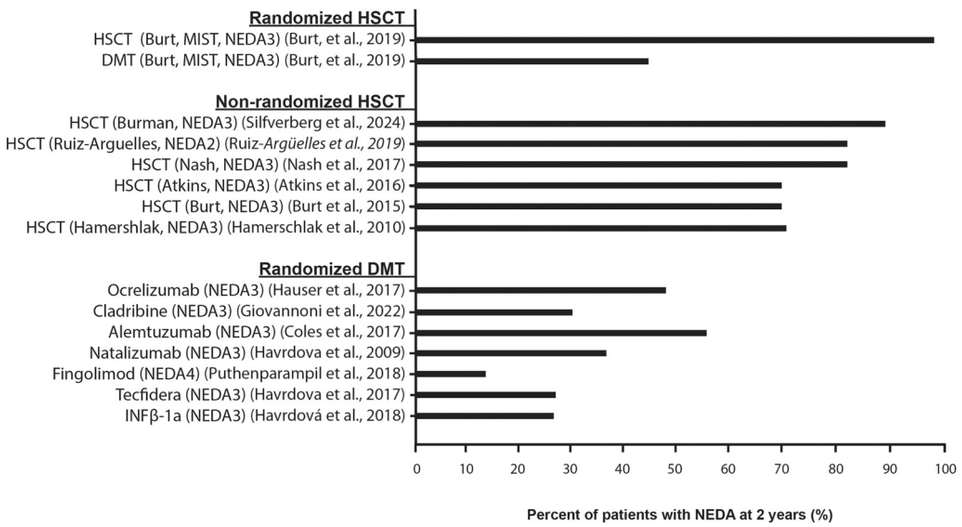
p0475 Myeloablative BEAM plus ATG was the most common regimen before 2010 (Sharrack et al., 2020). After 2010, nonmyeloablative cyclophosphamide and ATG became the most common regimen (Sharrack et al., 2020). Before 2010 progressive forms of MS were the most common indication for HSCT and the primary endpoint was PFS (Boffa et al., p0490 2021). After 2010, RRMS was the most common indication, and the primary endpoint shifted to sustained improvement in neurologic disability (Sharrack et al., 2020).

s0135 OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANTATION VERSUS DISEASE-MODIFYING THERAPIES

p0480 A summary of NEDA at 2 years for HSCT versus DMTs trials is shown in Figure 11.6. While comparison of published data strongly favors HSCT, comparison of HSCT to DMT data must include a caveat emptor asterisk. Except for the MIST trial, HSCT studies were nonrandomized, and some HSCT publications combine the results from RRMS and SPMS. Neither HSCT nor DMT studies included evaluation for paramagnetic rim lesions indicative of CALs that manifest as hypointense, ring-like structure on phase-sensitive imaging and predict for late accumulation of disability.

Within the field of HSCT, it remains unclear which HSCT regimen for MS is optimal and most balanced in terms of risk benefit (toxicity vs outcome). Several nonrandomized studies have suggested that a nonmyeloablative regimen of cyclophosphamide (200 mg/kg) and ATG (6.0 mg/kg) is safer and similarly efficacious in the near and intermediate term to BEAM/ATG (Hamerschlak et al., 2010; Saccardi et al., 2019; Sharrack et al., 2022; Jespersen et al., 2023; Silfverberg et al., 2024b). These publications are limited by nonrandomized results often from different time periods. Determining the optimal regimen is better addressed with randomized trials between HSCT and DMTs, between nonmyeloablative and myeloablative HSCT, and between two different nonmyeloablative regimens in centers that are experienced in using the same standard of care guideline mitigation strategies and patient selection.

In 2019, the randomized MIST trial demonstrated superiority of HSCT using a Cy/ATG regimen over best available therapy, mostly natalizumab that was the most effective DMT available at that time (Burt et al., 2015). In a 2021 retrospective nonrandomized analysis, HSCT using a BEAM/ATG regimen was reported superior to alemtuzumab (Häußler et al., 2021). There are now several randomized trials of HSCT versus best available DMT ongoing for RRMS (Sharrack et al., 2022). The United Kingdom StarMS and the Scandinavian RAM-MS trials are comparing a nonmyeloablative HSCT regimen (cyclophosphamide at 200 mg/kg and rATG at 6.0 mg.kg) to any of three (alemtuzumab, ocrelizumab, or cladribine) highly effective DMTs. The American BEAT-MS trial is comparing myeloablative BEAM/ATG to best available DMT. Unlike DMTs that are compared in randomized trials to a placebo or to the weakest (mildly effective) DMT, HSCT is compared to the best highly effective DMT (best available therapy).



f0035 **Fig. 11.6.** No evidence of disease activity (NEDA) at 2 years for disease-modifying therapy in RRMS or for predominately relapsing-remitting multiple sclerosis (>80% of patients) in the hematopoietic stem cell transplantation cohort. *NEDA2*, no clinical relapses and no progression, *NEDA3*, no relapses, no progression, and no new or enlarging lesions on routine MRI, *NEDA4*, no relapses, no progression, no new or enlarging lesions on routine MRI, and no new cortical lesions on double inversion recovery sequences. No studies included evaluation for paramagnetic rim lesions indicative of chronic active lesions that manifest as hypointense, ring-like structure on phase-sensitive imaging.

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p0490 Potential problems with these randomized trials arise from differences in experience and standard of care mitigation guidelines between transplant centers, limitations to completing enrollment due to failure to allow crossover, and bias in short- to mid-term outcomes due to PIRA. Each regimen has unique toxicities that require standardized training, experience, and optimal mitigation strategies.

p0500 Randomized trials not allowing crossover to the HSCT arm for defined failure of the DMT arm will diminish patient enrollment. Not allowing crossover is designed to allow long-term follow-up on each arm. However, since patients failing HSCT are allowed to p0525 receive DMT therapy, it seems inconsistent not to allow patients failing the DMT arm to crossover to HSCT which is also a DMT. Failure to allow crossover raises ethical concerns about equipoise in trial design (Freedman, 1987). If the study has a preordained intention to treat statistical analysis without defined crossover criteria, patients on the DMT arm who undergo HSCT elsewhere would continue to have their results reported to the DMT arm. PIRA especially with highly effective DMTs that suppress clinical relapse and MRI worsening when not evaluated for continued paramagnetic rim lesions may provide falsely reassuring midterm results (Kappos et al., 2020; Kuhlmann et al., 2023).

s0140 PRESENT STATUS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION

p0505 HSCT for inflammatory forms of MS was developed in centers s0150 worldwide from animal models to nonrandomized trials, to large p0530 meta-analyses, and a randomized controlled trial. Different immune reset regimens have been used by different authors. There have been no randomized trials between these regimens but a nonmyeloablative regimen appears safer with identical clinical improvements over at least the first few years. HSCT is a DMT. It is not a stem cell therapy. All immune-modulating therapies have toxicities and a place at the treatment table.

p0510 HSCT is a unique immune-modulating therapy because it reverses neurologic disability, significantly improves QOL, and patients enter drug-free prolonged remissions defined by NEDA. Compared to long-term DMTs, nonmyeloablative HSCT is markedly cost-effective. This therapy is best performed by a physician who specializes in both HSCT and in MS or alternatively a dedicated neurologist working seamlessly with a dedicated transplant hematologist.

s0145 SUMMARY

s0151 p0515 For relapsing MS, HSCT has stopped relapses, halted progression, p0531 reversed disability, improved QOL, and resulted in long-term treatment-free remissions despite initial morbidity. The field of HSCT was developed by dedicated academic-oriented hematolop0532 gists and neurologists. Awareness of HSCT depends solely on medical presentations and scientific peer-reviewed publications without resources or finances from the pharmaceutical industry as with the standard DMTs.

The terms DMT and HSCT likely contribute to confusion. DMTs are better defined as relapse-slowing therapy, or for highly effective DMTs, disability-slowing therapy. In contrast, HSCT may act as disability-reversing therapy, because it may reverse neurologic disability, improve QOL, and most patients enter drug-free prolonged remissions. The results of one randomized HSCT trial for RRMS can be used as proof of concept for "immune reset" for future HSCT trials or novel cellular therapies. However, each HSCT conditioning regimen ("the DMT") has different toxicities and efficacies. Ideally and importantly, each conditioning regimen should be proven in a separate randomized trial.

Despite these realities, the concept of using a conditioning regimen as a one-time DMT has changed the natural history of RRMS. Currently, there is no definition for a "cure" of MS. CSF oligoclonal bands remain the best diagnostic marker for MS (Schilke et al., 2023). Oligoclonal bands and a biomarker for axonal damage, neurofilament light, have been reported to disappear from the CSF of some patients approximately 8 years after HSCT (Larsson et al., 2020). Perhaps due to the results from HSCT for RRMS, it is time to consider proposing a working definition for cure for RRMS as a long-term, treatment-free, disease-free remissions defined by disappearance of oligoclonal bands and either NEDA-2 (no relapses and no progression) or NEDA-3 (no relapses, no progression, and no new MRI lesions).

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ABBREVIATION

2-CdA	cladribine
α4β1	α -4- β-1
ATG	antithymocyte globulin
BEAM	BCNU (carmustine), Etoposide, Ara-c (cytosine arabinoside), Melphalan
CAL	chronic active lesions
CD34	cluster differentiation 34, an antigen or epitope on hematopoietic stem cells
cGy	centigray
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
DMSO	dimethyl sulfoxide
DMT	disease-modifying therapy
DNA	deoxyribonucleic acid
DOD	department of defense
DODSR	department of defense serum repository
eATG	equine antithymocyte globulin
EBV	Epstein–Barr virus
EDSS	expanded disability status scale
EOMS	early-onset multiple sclerosis
FDA	Food and Drug Administration
Flu	influenza
GA	glatiramer acetate
GALA	glatiramer acetate low-frequency administration
G-CSF	granulocyte colony stimulating factor
HHV-6	human herpes virus 6
HLA	human leukocyte antigen
HSC	hematopoietic stem cells
HSCT	hematopoietic stem cell transplantation
HSV	herpes simplex virus
HTN	hypertension
IL	interleukin
IFN	interferon

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IFN-β	interferon β
IFN-γ	interferon γ
ITP	idiopathic thrombocytopenic purpura
IV	intravenous
JCV	John Cunningham virus
MIST	multiple sclerosis immune suppression versus transplant trial
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSCRG	Multiple Sclerosis Collaborative Research Group
NCI CTCAE	National Cancer Institute Common Toxicity Criteria Adverse Events
NEDA	no evidence of disease activity
NEDA-2	no evidence of disease activity, no relapses, no progression
NEDA-3	no evidence of disease activity, no relapses, no progression, no MRI activity
NEDA-4	no evidence of disease activity, no relapses, no progression, no MRI activity, no cerebral atrophy (beyond normal aging)
PBSC	peripheral blood stem cells
PCR	polymerase chain reaction
PFS	progression-free survival
PIRA	progression independent of relapse activity
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
QOL	quality of life
rATG	rabbit antithymocyte globulin
RBC	red blood cell
RFS	relapse-free survival
RRMS	relapsing-remitting multiple sclerosis
sc	subcutaneous
S1P	sphingosine-1-phosphate
SPMS	secondary progressive multiple sclerosis
TBI	total body irradiation
TEN	toxic epidermal necrolysis
Th	T helper
TIW	three times a week
Treg	T regulatory (cells)
URTI	upper respiratory tract infections
UTI	urinary tract infection
UV	ultraviolet
VZV	varicella zoster virus

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