Severe, Highly Active, or Aggressive Multiple Sclerosis

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ABSTRACT

Purpose of Review: Despite the efficacy of current therapies for relapsing forms of multiple sclerosis (MS), there remains a group of patients whose disease fails to respond and warrants a different approach to treatment. This article reviews this form of aggressive MS and proposes a definition and new treatment algorithm. Failing to recognize aggressive MS and initiate more effective therapy will result in a lost opportunity to effectively treat the disease.

Recent Findings: Natural history studies, together with the results of contemporary clinical trials, help to identify and profile a subset of patients with relapsing MS who have a much poorer prognosis and for whom conventional treatment tends to fail. Therapies that have shown success in the treatment of this patient group with aggressive MS are reviewed and discussed.

Summary: It is imperative to recognize aggressive MS to effectively treat it before patients progress. Recognizing aggressive MS as early as possible is the key to successful implementation of a proposed algorithm.

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Unlabeled Use of Products/Investigational Use Disclosure: Drs Freedman and Rush discuss the unlabeled/investigational use of ocrelizumab, parenteral cladribine, rituximab, and stem cell transplantation for the treatment of aggressive multiple sclerosis.

INTRODUCTION

Although some controversy still exists, most believe that multiple sclerosis (MS) is a disease of the central nervous system (CNS) propagated by CNS-directed autoimmunity that early on is characterized by inflammation, demyelination, and axonal transection.[1] As the disease evolves, so does the pathology, and a more diffuse and indolent inflammatory pathology is noted, characterizing the neurodegenerative phase of disease, which to date lacks effective treatment.[2]

A number of disease-modifying therapies have been approved for the treatment of relapsing forms of MS with variable success at controlling the early type of inflammatory events. However, no treatments exist that can stop or reverse the later type of pathology characterizing the neurodegenerative phase or its clinical counterpart, progressive MS (either primary or secondary). Natural history studies repeatedly inform us that patients with greater amounts of early disease activity are more likely to advance to the progressive phase earlier and faster.[3–5] Conversely, studies have shown that early introduction of effective therapy may well stave off the progressive phase.[6] It is therefore imperative that effective early treatment be optimized to take advantage of the window of opportunity[7] before it closes and patients transition from relapsing to progressive disease.

Before the development of disease-specific therapies for MS, treatment was confined to the use of immunosuppressive agents, limited in dose

KEY POINTS

- The window of opportunity for effective early treatment in multiple sclerosis is unique for each patient. It most likely opens after the first attack in clinically isolated syndrome and closes at transition from relapsing multiple sclerosis to secondary progressive multiple sclerosis or late relapsing-remitting multiple sclerosis in which the presence of relapses, MRI activity, and inflammation is no longer evident.
- The perception that current disease-modifying therapies are effective in all patients with relapsing multiple sclerosis needs to be dispelled. All studies include patients with considerable breakthrough disease that warrant a different approach.
- The ideal monitoring schedule for relapsing multiple sclerosis (both clinical and MRI) is not agreed upon; it depends on the level of concern for each patient, based on relapses, MRI activity, changes in neurologic examination, and availability of resources.

and duration of treatment by their inherent toxicities. At best, such treatment approaches seemed to "buy a few years" of time for patients before the return of disease activity, but in general, and in part due to their toxicities, they were introduced rather late in the course of disease. Today's disease-specific therapies are not hampered, for the most part, with lifetime limitations in dosage, allowing for a more continued approach to treatment. Furthermore, many have fewer toxicities compared with older immunosuppressive treatments and can be introduced early in the disease course, when they are likely to make the biggest difference. Based on the premise of controlling the important early inflammation in MS, it is imperative that treatments get a foothold on the disease without sacrificing safety or tolerability in often young patients. Current disease-modifying therapies are concentrated on controlling, segregating, blocking, or depleting disease-causing autoimmune cells, thus limiting their ability to enter and damage the CNS. They do so by various proposed mechanisms of action. Unfortunately, not a single one of today's disease-modifying therapies has been shown to completely control disease activity in all patients, even within the narrow window of a 2-year clinical trial. A subset of those patients is emerging as having a more aggressive form of disease, warranting perhaps a different approach.

Several treatment algorithms have been proposed for patients with relapsing forms of MS that focus on the typical patient, starting with the modestly effective but safe first-line treatments and switching either laterally to an alternate first-line agent or moving to a second- or even third-line disease-modifying therapy if the response to therapy is suboptimal.[8–10] This approach should be adequate for most patients today and maximizes the benefit to risk of disease-modifying therapy, provided that patient monitoring is adequate. However, for the subgroup of patients with a more aggressive and rapidly deteriorating course marked by rapid accumulation of physical and cognitive deficits despite attempted treatment with one or more disease-modifying therapies, such an approach is clearly suboptimal. This subgroup of patients is often referred to as having aggressive MS, but no consensus definition or approach to treatment exists for these patients. Over the years, many have come to recognize the existence of this subgroup of aggressive MS, but definitions have been either vague or ambiguous. Common to all is the somewhat unexpected appearance of early advancing disability, often with frequent disabling relapses that have incomplete resolution, and highly active MRI measures. Pragmatically, aggressive MS has been defined as MS that is associated with repeated severe attacks with accelerated accrual of disability or, more simply, rapidly progressive MS. The literature also harbors the term *malignant MS*, but this defines a heterogeneous group of patients. Some use malignant to describe fulminant forms of MS that deteriorate so rapidly and progressively from the beginning that they are almost monophasic illnesses and can result in death within a very short time (ie, the Marburg variant of MS).[11] This probably represents the most extreme variant of the aggressive MS spectrum, but others may use the term malignant interchangeably with what will be referred to here as aggressive MS. In its first rendition, a report on defining the clinical phenotypes of MS included a definition of malignant MS[12] as a "disease with a rapid progressive course,

leading to significant disability in multiple neurologic systems or death in a relatively short time after disease onset." This committee, however, despite recent and increasing concern for early detection and treatment of aggressive MS, did not update its original definition of malignant MS in its latest version.[13]

More succinct attempts at defining aggressive MS have been made. Some researchers described malignant MS as a subgroup of patients attaining an Expanded Disability Status Scale (EDSS) score of 6.0 within 5 years of MS onset.[14] They found that only 12.11% of their 487 patients had malignant MS, which was further divided into transient malignant and sustained malignant based on whether it was relapse or progression that was the main contributor to the EDSS score. Being older, male, or a smoker made patients more likely to attain sustained malignant status. Conversely, younger patients with brainstem relapses characterized the transient malignant subgroup, identifying specific clinical features for which opportune intervention might make a difference.

In a 2013 study from British Columbia, the definition of aggressive MS was expanded by defining three subgroups of criteria, used alone or in combination, based on EDSS score and time to progression to secondary progressive MS.[15] Aggressive MS was defined using three slightly different definitions depending on the rapidity of disability accumulation. Aggressive MS1 (AMS1) reached confirmed EDSS score of 6.0 or more within 5 years from the onset of MS symptoms, aggressive MS2 (AMS2) reached confirmed EDSS score of 6.0 or more by age 40, and aggressive MS3 (AMS3) reached secondary progressive MS within 3 years of a relapsing onset course. Out of a database of 5891 patients, 5.5% fulfilled criteria for AMS1, 14.0% for AMS2, and 4.0% for AMS3. Most important with respect to treatment considerations, of the first two definitions, which could include primary progressive MS, 74.5% of AMS1 and 92.8% of AMS2 were, in fact, relapsing-onset patients. Thus, aggressive MS could be identified in 4% to 14% of patients, depending on the definition used; the majority of these are relapsing forms of MS and therefore amenable to treatments that can target early inflammation.

Another definition for aggressive MS was used to identify eligible candidates for a trial of immunoablative therapy followed by autologous hematopoietic stem cell rescue or transplantation. This international consortium referred to these patients as having highly active MS and at higher risk of poor prognosis. That definition combines the failure of conventional treatment to control disease with frequent severe (disabling) relapses and MRI activity (new T2 or gadolinium-enhancing lesion).[16] In addition, however, patients considered for this type of treatment are also typically restricted by age, EDSS score, and duration of MS or time from first treatment.

Any definition for aggressive MS needs to be both sensitive and specific, but sensitivity is probably more important. It is likely acceptable today to overtreat some patients who might not truly have aggressive MS in favor of not missing anyone warranting treatment to prevent the inexorable progressive phase of disease. Previous definitions are probably too restrictive, sacrificing sensitivity for specificity in too often failing to identify at-risk patients who should be offered potentially helpful yet aggressive treatments. No consensus exists on how fast progression should occur or a threshold of disability attained, but probably most consider that reaching an EDSS

KEY POINT

- To date, aggressive multiple sclerosis has no uniform definition.

KEY POINT

■ Multiple sclerosis has several well-known clinical and MRI factors for poor prognosis.

score of 6.0 represents an upper limit beyond which the benefit to risk of an aggressive treatment is likely not warranted. Others have argued that attaining even an EDSS score of 4.0 is already a strong indicator of advancing disease and that further relapses, even if prevented, are unlikely to change the course of progression.[3] Therefore, no perfect definition exists, but in an attempt to reasonably describe a population that could warrant a more aggressive approach to therapy, it is suggested that aggressive MS be defined as a relapsing form of MS with one or more of the following features:

- EDSS score of 4.0 within 5 years of onset
- Poor response to at least 1 full year of therapy with one or more disease-modifying therapies, not because of intolerance
- Breakthrough disease over at least 1 year of disease-modifying therapy consisting of:
  - Two or more disabling relapses with incomplete resolution
  - Two or more MRI studies showing new or enlarging T2 lesions or gadolinium-enhancing lesions

Studies now have identified a number of poor prognostic factors that undoubtedly will also characterize many patients with aggressive MS. These include male gender; older age at onset; multifocal attacks involving motor, cerebellar, or sphincter function; and cognitive involvement. Historical attack characteristics may also provide additional prognostic information: multifocal versus monofocal, motor versus sensory, residual deficits unresponsive to steroids,[17] and greater effect on activities of daily living.[18–20] Certain MRI characteristics have also been associated with a poorer prognosis, especially early in the course of disease, such as T1 black holes at presentation,[21] T2 burden,[22–24] early presence of atrophy,[25,26] or even location of the burden of lesions (eg, brainstem and spinal cord).[27,28] Although useful, these MRI metrics have not yet been shown to particularly distinguish an aggressive pattern of disease in the absence of concurrent clinical information either at disease onset or early in the course of disease (**Table 4-1**).

THE NEED FOR EARLY DISEASE CONTROL

It is becoming clearer that active early MS, although seemingly controllable, takes its toll and leads to earlier progression. A number of mechanisms contribute to this, such as the inability to repair early damage or the degree to which an individual's CNS can withstand injury. However, one of the most important factors may well be the loss of CNS reserve that gets tested as a patient begins to age. Studies have repeatedly shown that uncontrolled disabling relapses that occur in the first 2 years of disease hasten early disease progression, with diminishing contribution from later relapses as the disease progresses.[17,29] Data derived from patients followed long term from their first demyelinating event as well as data from one of the pivotal long-term trial cohort studies suggest that long-term outcomes can be predicted based on factors present early in the disease. The time to an EDSS score of 3.0 is a strong independent determinant of time to later EDSS scores of 6.0, 8.0, and 10.0 (death due to MS).[29] The inability to contain the early damage or heal to recovery is noted in patients with high attack rates and shorter interattack intervals who convert within a shorter time to secondary progressive MS. The amount of silent disease, as manifested by the first MRI at the time

TABLE 4-1 Factors Associated With a Poorer Prognosis in Multiple Sclerosis

- ▶ **Demographics**
  - Male
  - Older than 40 years at onset
  - African American, African Latin American
- ▶ **Relapse Characteristics**
  - Severity of relapse
    - Moderate/severe (≥1 point change on EDSS or ≥2 point change on any individual KFS, or ≥1 point change on any two KFS)
    - Steroid requirement
    - Hospital admission
  - Type of attack
    - Multifocal
    - Partial or incomplete recovery
    - Affecting motor, cerebellar, sphincteric, or cognitive functions
  - Frequency
    - Frequent relapses in the first 2–5 years
    - Short interattack interval
- ▶ **Disease Course**
  - Rapid accrual of disability (EDSS of 3.0 within 5 years with superimposed relapses)
  - Progressive from onset
- ▶ **MRI Features**
  - At onset
    - High T2 lesion burden
    - More than two gadolinium-enhancing lesions
    - Presence of T1-hypointense lesions (black holes)
    - Early discernable atrophy
    - Infratentorial versus supratentorial lesions
  - Follow-up MRI while on treatment
    - Presence of new T2 lesions
    - More than one gadolinium-enhancing lesion

EDSS = Expanded Disability Status Scale; KFS: Kurtzke Functional System; MRI = magnetic resonance imaging.

KEY POINTS

- Effectively treating multiple sclerosis early preserves central nervous system reserve for aging later in life.
- The ideal sequence in which multiple sclerosis treatments should be used has not been clearly explored. The sequence may predispose patients to increased risk of toxicity due to compounded side effects and limit the successive use of certain agents.

of first presentation, correlates with the degree of disability seen up to 20 years from that heralding first event.[30] In patients converting from relapsing-remitting MS to secondary progressive MS, the rate of lesion volume change was 3 times higher than those who did not convert.

If early inflammation eats up CNS reserve and current medications are most effective at reducing this inflammation, then it makes sense to maximize the treatment effect when inflammation is at its peak. Therefore, a window of opportunity for optimizing treatment opens once it is clear that a patient has MS, likely following the first clear demyelinating event.[31] One could equally argue that once this inflammation subsides, it probably indicates that the window has closed and likely the patient has entered the secondary progressive MS phase of disease. While the search for effective therapeutic strategies for secondary progressive MS continues, it is fairly obvious that most agents demonstrated to be effective at controlling relapsing MS are ineffective at slowing progression in secondary progressive MS, notwithstanding their ability to reduce attack rates or limit MRI activity. Patients with aggressive MS will have a narrower window that can close quickly and therefore warrant a different approach. Conventional treatment paradigms developed for relapsing MS need to be reconsidered. The normal move to escalate treatment only after failure of a less effective disease-modifying therapy could lead to a missed opportunity to identify and treat aggressive MS in a timely manner. Similarly, we must avoid the ineffective use of more aggressive treatments that offer "too little too late" in terms of efficacy once disease has evolved beyond the stage of relapsing MS, but whose risks may still be formidable, thus presenting a poor risk-benefit ratio.

TREATING AGGRESSIVE MULTIPLE SCLEROSIS

We have now an array of effective treatments for relapsing MS; however, choosing the best sequence for an individual can be very challenging. Do we simply start with the safest, but possibly least effective, treatments and escalate only when breakthrough disease is evident? Or is there some way of identifying patients who may warrant a more aggressive approach, starting with perhaps riskier but perceived more effective therapies and either maintaining them or backing down to the safer treatments once it is evident that disease is well controlled? Fortunately, for most relapsing MS, an escalation approach is effective, but for aggressive MS, it clearly is not. Once identified, patients with aggressive MS warrant a sustained effort to control disease activity in an attempt to stave off imminent disease progression.

By definition, patients with aggressive MS are identified by an early failure to control disease activity with conventional first- or even second-line agents. If one can imagine a rogue force of aberrant disease-causing inflammatory immune cells whose mission is to attack CNS myelin and which can self-renew *ad infinitum*, then part of the reason for failure of the usual relapsing MS treatments is that they fall short in reducing the size of this force. Even therapies that either impede the force of disease-causing cells from gaining access to the CNS (eg, natalizumab) or sequester the force in lymph nodes (eg, fingolimod) will fail in patients with aggressive MS, most of whom will have been tried on one or both of these types of treatments. Treating aggressive MS requires

agents immediately capable of significantly depleting the force of disease-causing cells; these include agents such as alemtuzumab; chemotherapeutic treatments such as cladribine, cyclophosphamide, or mitoxantrone; and even a full-on assault using immunoablation and autologous hematopoietic stem cell transplantation.

Patients with aggressive MS are at high risk of further imminent progression and are rapidly running out of time (ie, their window is closing). They therefore warrant a more definitive treatment, not a temporary fix. First-line agents will have failed, and current second-line agents, such as fingolimod or natalizumab, exert disease control as long as they are maintained, but both are associated with a return of disease activity if they are stopped. A gradual return of activity is seen with fingolimod discontinuation,[32,33] but a rapid, sometimes severe, rebound of disease activity is observed with stopping natalizumab, which can be fatal, especially in patients with aggressive MS.[34,35] The likelihood of achieving the goals for treatment of aggressive MS is low, with fingolimod providing the only partial benefit observed for patients with highly active relapsing MS seen in clinical trials.[36] Similarly, although natalizumab has been used anecdotally in some patients with aggressive MS,[37] the propensity for harm in the development of progressive multifocal leukoencephalopathy with extended use and the potential for severe rebound should the drug be stopped suddenly are both limiting factors. Fingolimod too is now associated with the development of progressive multifocal leukoencephalopathy, although as yet no clear identifying factors have been found to offset the risk. Both therapies must therefore be viewed as unsustainable in the long term.

Drugs Considered for Treating Aggressive Multiple Sclerosis

The following treatments (**Table 4-2**[38–56]) all share the ability to significantly deplete disease-causing autoimmune cells. In many cases, they still do not eliminate all the cells; what differentiates them is the length of time required before the cells come back and disease activity returns. In some cases, it may be possible for retreatment with another course of the same therapy, but in other cases, especially where cumulative dosing leads to toxicity, this may not be possible. Given the propensity for a return of disease activity, some feel that a first-line disease-modifying therapy may be used following the initial treatment of aggressive MS with one of these agents to extend the initial benefit or even maintain it; but thus far little evidence exists to support this strategy beyond anecdotal reports.

Alemtuzumab. Alemtuzumab is a humanized monoclonal antibody directed against CD52, a surface antigen present at high levels on T and B lymphocytes. Alemtuzumab rapidly depletes lymphocytes, producing a sustained depression for up to 1 year.[38,57] It is approved mainly for patients with relapsing MS with breakthrough disease but is proven ineffective for secondary progressive MS.[58] It is viewed as probably the most useful current therapy as an induction agent in the treatment of aggressive MS, especially in Europe.[59] Although trials attest to its benefit in both naïve and breakthrough patients, with an effect on slowing disease progression and actually improving EDSS score, especially in breakthrough patients compared directly with a first-line high-dose interferon treatment,[39] there is still little experience in aggressive MS. The biggest concern with alemtuzumab is the

KEY POINTS

- Effective treatment for aggressive multiple sclerosis requires the depletion of disease-causing immune cells.
- Aggressive multiple sclerosis warrants aggressive treatment. These patients are running out of biological time and have a narrower therapeutic window.

TABLE 4-2 Drugs to Treat Aggressive Multiple Sclerosis

Drug	Protocol	Adverse Effects Not Directly Related to Immunosuppression	Monitoring
Alemtuzumab[38,39]	12 mg/d infusion for 5 days followed by second course of 12 mg/d for 3 days at month 12 from first course	Infusion-related reactions 93% Mild to moderate >90% Serious 3%	Follow treatment protocol, symptomatic management
	Retreatment with a 3-day course in the third or subsequent year as dictated by continued disease activity	Infections 71% Serious infections 2.7% Nasopharyngitis Upper airway tract infections Urinary tract infections	No specific recommendation, patient education
		Superficial fungal infections 12% Oral candidiasis Vaginal candidiasis	No specific recommendation, patient education
		Herpesvirus infections 3% Oral herpes simplex Varicella-zoster infections 0.3%	No specific recommendation, patient education
		Cervical human papilloma virus infection 2%	Annual screening for human papilloma virus
		Thyroid problems 36% Hyperthyroidism Hypothyroidism Graves disease Thyroid ophthalmopathy Thyroid cancer 0.3%	Thyroid-stimulating hormone and free T4 every 3 months for 48 months after the final infusion, monthly symptom-monitoring survey
		Hematologic problems 1% Idiopathic thrombocytopenic purpura Other cytopenias (neutropenia, hemolytic anemia, pancytopenia)	Monthly blood cell count with differential and platelet counts, symptom-monitoring survey, patient education
		Nephropathies 0.3% Anti–glomerular membrane Membranous glomerulonephritis	Monthly serum creatinine and urinalysis with microscopy, monthly symptom-monitoring survey, patient education

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TABLE 4-2 Drugs to Treat Aggressive Multiple Sclerosis *Continued from page 768*

Drug	Protocol	Adverse Effects Not Directly Related to Immunosuppression	Monitoring
Cladribine[40,41]	Scripps protocol: 0.875 mg/kg/d IV for 4 days every 6 months for 2 years Retreatment with two 6-month cycles in the third or subsequent year as dictated by continued disease activity	Possible long-term risk of malignancy	Cancer screening, patient and primary physician education
Mitoxantrone	Mitoxantrone In Multiple Sclerosis Study Group (MIMS) protocol[42]: 12 mg/m^2 IV every 3 months for 24 months French British Study Protocol[43]: 12–20 mg/month IV + 1 g/month methylprednisolone IV for 6 months Lifetime maximum: 140 mg/m^2	Gonadal failure	Symptomatic management, patient education, fertility preservation techniques prior to treatment
		Amenorrhea in 22–26%[44,45]	Symptomatic management, patient education, fertility preservation techniques prior to treatment
		Liver toxicity	Liver function monitoring (aspartate aminotransferase and alanine transaminase)
		Cardiotoxicity[46] Systolic dysfunction 12% Cardiotoxicity 10% Heart failure 0.4%	Echocardiogram or multigated acquisition scan (MUGA) annually for 5 years posttreatment
		Leukemia 1%[46]	Blood cell counts every 6 months for 5 years
Cyclophosphamide[47]	Induction protocol[48]: 600 mg/m^2 IV for 5 days plus 1 g methylprednisolone IV and bimonthly boosters Pulse protocol[50]: 800–1000 mg/m^2 (with or without methylprednisolone) IV monthly for 12–24 months High-dose protocol[52]: 120–200 mg/kg/d IV for 5 days Lifetime maximum: 80–100 g[54]	Hemorrhagic cystitis 7–15%[49]	Prevention with adequate pre- and post-IV hydration, mesna, and frequent voiding or bladder catheterization if needed
		Bladder cancer 5.7%[51]	Urinalysis and cytology every 6 months; if cytology is abnormal, perform cystoscopy annually
		Infertility 33–44.7%[53]	Symptomatic management, patient education, fertility preservation techniques prior to treatment
		Brain atrophy[55,56]	Role for neurocognitive assessment

IV = intravenous.

emergence of autoimmune disorders unrelated to MS (eg, thyroid disease, idiopathic thrombocytopenic purpura, or Goodpasture syndrome) that can arise remotely (up to 4 years from the last exposure) regardless of whether one or many treatment courses are given.[60] Fortunately, all of these can be easily detected with proper monitoring. A course of treatment with alemtuzumab entails 5 consecutive days of treatment in the first year and 3 consecutive days in the second year. Unlike the other agents with maximal lifetime exposure limits, it appears that alemtuzumab can be used beyond 2 years intermittently as needed should the disease return, as a 3-day annual treatment, as long as more than 1 year has passed from the last treatment and the lymphocyte count has returned to normal. Data from extension studies of the phase 3 trials (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis [CARE-MS] I and CARE-MS II) showed that more than 80% of patients did not require retreatment during the third year, but these studies comprised mostly patients without aggressive MS.

Cladribine. Cladribine is a synthetic purine nucleoside and antimetabolite that acts as an antineoplastic agent with immunosuppressive effects. It selectively reduces lymphocyte subpopulations, especially CD4+ and CD8+ because these subsets of T cells lack alternative degrading enzymes, leading to cell-selective sequestration of the nucleoside. Animal data exist showing it is capable of crossing the blood-brain barrier.[61]

Parenteral cladribine was found to be beneficial in early phase 2 studies in relapsing-remitting MS,[41,62] but not in secondary progressive MS.[40] Oral cladribine was studied in the Cladribine Tablets Treating MS Orally (CLARITY) study,[63] which included more than 1000 patients and compared two different doses over 96 weeks. Although both doses produced a significant reduction in clinical relapses and MRI activity and slowed disease progression, the higher dose showed no particular benefit, even in a subgroup of patients with highly active MS. Oral cladribine was subsequently studied in a select group of patients with more active MS who had breakthrough disease on interferon beta in a study called Oral Cladribine Added ON to Rebif New Formulation in Patients With Active Relapsing Disease (ONWARD), in which patients taking cladribine together with interferon beta had fewer subsequent relapses and gadolinium-enhancing lesions compared to the arm taking interferon beta alone, despite the study not being powered for these outcome measures. The combination of cladribine and interferon beta also showed a greater reduction of relapse relative to placebo following a first demyelinating event (clinically isolated syndrome) than any other treatment used at this stage of disease.[64]

Although clinical development of oral cladribine has remained on hold, parenteral infusions can still be readily used. Most commonly, cladribine is given as an initial 2-year course, starting with an induction therapy over 4 consecutive days and repeated every 6 months. Patients can then be followed and a repeat 1-year course of treatment offered should disease activity rekindle, as long as lymphocyte levels have recovered and it has been more than 6 months since the last treatment. Alternatively, cladribine can be followed by a first-line treatment to sustain the benefits, although scant data are available to support that option.

Cladribine remains an option for treating aggressive MS but can be a

complicated treatment with significant toxicity, so it is best given in centers where hematologic expertise and support is available. It has at least some advantage over other similar agents listed later because it does not negatively affect fertility, but its long-term safety in MS is unknown.

Cyclophosphamide. Cyclophosphamide is a broad-spectrum alkylating compound used in cancer and autoimmune diseases. It is a cell cycle nonspecific cytotoxic agent that exerts its effects on both B cells and T cells, suppressing both humoral and cell-mediated immunity.[48] It has been used in various regimens to treat MS for the past 40 years.

Early studies, mainly in patients with progressive MS, produced conflicting results at slowing disease progression. Then a 2-year randomized trial of 256 patients with relapsing MS using different regimens of cyclophosphamide induction followed or not by monthly infusions of cyclophosphamide reported that treatment with the cyclophosphamide boosters was associated with better disease stabilization; especially in younger patients who had only recently converted to secondary progressive MS.[65] Over the years, many small, often single-center, studies have demonstrated a potential benefit of cyclophosphamide in refractory, fulminant, or rapidly progressing patients in at least temporarily slowing down disease progression or limiting further disabling attacks for 12 or 24 months, depending on the study.[47,50,52] Some interest was given to a regimen termed *High Cy*, which professed to be immunoablative (as opposed to myeloablative; refer to the later discussion of autologous hematopoietic stem cell transplantation),[66,67] producing clinical and radiologic stability that could last more than 3 years.[68] A small study of patients with aggressive MS refractory to several previous therapies received monthly cyclophosphamide infusions and were shown to have a dramatic reduction in gadolinium-enhancing and T2 lesion load.[53] This result was reiterated by a subsequent study where gadolinium-enhancing lesions decreased by 81% over 2 years,[69] along with other reports of combination studies of cyclophosphamide (often in association with interferon beta) that showed significant efficacy in reducing MRI activity.[70,71]

Cyclophosphamide has significant toxicity with limitations on lifelong cumulative dose (around 80 g to 100 g). Increased risk of malignancy (in particular bladder cancer), hemorrhagic cystitis, and gonadotoxicity are the most feared side effects. The risk of bladder cancer with cyclophosphamide has been found to be similar to the general population, contrasting with older studies, perhaps because of the use of parenteral cyclophosphamide instead of the oral formulation used in the past.[72] Experience with the various regimens dictates which one may be used, but no evidence exists that any one is superior to another.

Despite the known downside of cyclophosphamide, attestations to its efficacy, low cost, extensive availability, and experience keep it on the list of potentially useful agents for treating aggressive MS.

Mitoxantrone. Mitoxantrone is an anthracenedione similar to doxorubicin. It inhibits proliferation of B cells and T cells and suppresses T_H1-mediated cytokines (eg, tumor necrosis factor [TNF]-α, interleukin [IL]-12).[73] Most patients benefiting from mitoxantrone in the pivotal trials were young, had frequent relapses and lower EDSS scores, or had an early secondary progressive MS or relapsing MS/aggressive MS diagnosis.[42,43]

KEY POINT

■ Cyclophosphamide has been resurrected in the treatment of multiple sclerosis and has a valid position in our current armamentarium as induction therapy in aggressive multiple sclerosis.

KEY POINT

■ Despite its more common use for aggressive multiple sclerosis more than a decade ago, mitoxantrone has fallen considerably out of favor because of its dose-dependent cardiotoxicity and more idiosyncratic tendency to leukemia, but it still remains an option should other modalities fail or if other options are unavailable.

Mitoxantrone has a moderate effect at reducing disability progression and relapses in patients with persistent inflammatory activity. The most commonly used regimen is the induction protocol (three doses of 12 mg/m^2 monthly followed by six monthly infusions of the same dose until a maximum of 110 mg/m^2 to 120 mg/m^2 has been reached). Cumulative lifetime doses should not exceed 140 mg/m^2. Gonadal dysfunction is a relevant toxicity in young patients. A full course of treatment can stabilize patients with aggressive MS for 5 years or more,[74] but if maximal lifetime doses are reached, then patients might be better off following the treatment with maintenance of a first-line agent such as interferon beta[75] or glatiramer acetate.[76,77]

Despite its more common use for aggressive MS more than a decade ago, mitoxantrone has fallen considerably out of favor because of its dose-dependent cardiotoxicity and more idiosyncratic tendency to leukemia, but it still remains an option should other modalities fail or if other options are unavailable.

Rituximab. Rituximab is a partially humanized monoclonal antibody targeting the CD20 antigen on B cells producing depletion of circulating B cells.[78] Although somewhat extensively used off-label in many parts of the world for refractory MS, it has only been tested in small short-term studies, but a similar agent called ocrelizumab[79] has completed two large randomized studies in relapsing MS. Some of the data revealed that mostly naïve patients in both studies showed an excellent therapeutic effect of ocrelizumab treatment on relapse rate reduction, slowing of disease progression, and suppression of MRI activity compared to active therapy with subcutaneous interferon beta-1a 3 times a week over 2 years, but there were no data on subsets of patients that might be deemed as having aggressive MS. Regulatory bodies will review the study data to determine whether this will be positioned as first- or second-line therapy.[80] Smaller studies with rituximab have also been encouraging, demonstrating a powerful effect on MRI activity.[81,82] Based in part on a theory that the presence of B-cell follicles in the meninges[83] contributes to disease progression, rituximab was tested in a large clinical trial in primary progressive MS and failed to slow progression in the entire study group, although a subgroup of younger patients with enhancing lesions might have benefited.[84] A similar study with ocrelizumab reported a successful overall delay in disease progression of patients with primary progressive MS, but it is not known whether this was all driven by younger patients with continued evidence of inflammation as some 25% of patients had gadolinium-enhancing lesions at baseline.[85] In other conditions, such as rheumatoid arthritis, periodic rituximab treatment could successfully control disease with or without using concurrent agents.[86]

Rituximab is discussed here because it has been used anecdotally to treat aggressive MS in many parts of the world, despite the lack of supporting data. However, we are not advocating for its use, rather just acknowledging that some have used it rather than the other agents listed here.[87] Without the level of evidence that can only be derived from properly conducted controlled trials, we would not consider it an alternative to the other proposed treatment choices.

Immunoablation and Autologous Hematopoietic Stem Cell Transplantation

Intensive myeloablative or immunoablative conditioning treatment with

various regimens of chemotherapy followed by a rescue imparted by autologously derived hematopoietic stem cells has been used successfully for the past 2 decades to treat severe treatment-refractory autoimmune diseases, including MS. More than 800 patients with MS around the world have been treated with autologous hematopoietic stem cell transplantation using various regimens.[88] Earlier studies that selected patients who were more severely disabled to establish the safety of the procedure not surprisingly showed little in the way of efficacy, but a high morbidity and mortality (approximately 5%) was seen, probably owing to the poorer clinical state of these patients with advanced disease. Mortality rates were approximately 5% in the early transplant era. Other trials have focused more on patients with highly active disease that was refractory to conventional disease-modifying therapy, and demonstrated much more encouraging safety data (mortality less than 1%).[88] The rationale for this severe approach rests in the ability of this treatment to produce a complete immune system reset, effectively eradicating the disease-causing immune cells using intense immunosuppression and reestablishing a new immune system derived from autologous stem cells.[89] The newly developing immune system leads to immune tolerance, devoid of disease-causing autoreactive cells. Furthermore, the more definitive ablative regimens produce long-lasting remissions without the need for further treatment with disease-modifying therapy.

The problem is that several transplant conditioning regimens are used among different transplantation groups, and no consensus exists that one protocol is superior. Although it is uncertain whether the intensity of the conditioning (ablative) protocol influences the outcome, nonmyeloablative regimens trade reduced toxicity for reduced efficacy in halting MRI activity or stopping relapses,[90] with one of the largest studies showing an 80% relapse-free survival over 4 years and significant improvement in EDSS scores in a majority of patients with this regimen.[91] The 3-year interim report of the High-dose Immunosuppression and Autologous Stem Cell Transplantation for Multiple Sclerosis (HALT MS) study in North America used a medium-intensity conditioning protocol and demonstrated that 86.6% of patients were relapse free with a progression-free survival of 90.9% over 3 years.[92] The European study used a similar conditioning protocol, randomly assigning patients to autologous hematopoietic stem cell transplantation versus mitoxantrone, but recruitment was so dismal over the years that they changed their primary outcome to MRI measures and curtailed the study early. However, the study did show the superiority of autologous hematopoietic stem cell transplantation versus mitoxantrone in reducing MRI activity and relapses.[93] Our own experience, using a much higher myeloablative conditioning regimen and a CD34+ selected graft to treat aggressive MS, showed that 100% of patients followed for more than 10 years from transplant were free of relapses or new MRI activity. Many actually improved, but approximately 30% progressed despite the fact that no further inflammatory activity was detected.[94]

Increasing expertise and promising results have sparked multinational efforts and even a consensus on how to further investigate the role of autologous hematopoietic stem cell transplantation in aggressive MS and to assess long-term efficacy and safety.[16] Still, this type of treatment should be reserved

KEY POINTS

- Limited, but promising, evidence exists for use of autologous hematopoietic stem cell transplantation in severe neurologic conditions with immune basis other than multiple sclerosis (eg, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, stiff person syndrome, neuromyelitis optica, and autoimmune encephalitis).
- It is possible to completely or almost completely remove an entire immune system and replace it with a new one that may no longer attack the central nervous system.

KEY POINTS

- Autologous hematopoietic stem cell transplantation should be performed only in centers with extensive hematologic and neurologic experience in this treatment and the management of patients after bone marrow transplantation, as specific issues and complications may be seen in multiple sclerosis patients undergoing this procedure.
- ''No evidence of disease activity'' (NEDA) is a composite of absence of clinical relapses, MRI activity (new or enlarging T2 or gadolinium-enhancing lesions), and disability progression.

for centers with established experience in bone marrow transplantation.

Changing the Treatment Paradigm of Aggressive Multiple Sclerosis

Classically, the paradigm of starting with safer agents in early phases of disease, then escalating to medications with presumed greater efficacy but proven greater toxicity only after a suboptimal response followed by either maintenance or deescalation after a period of stability is appropriate for most patients with relapsing MS. This conservative approach prioritizes safety over possibly greater efficacy and can be quite effective provided that patients are closely monitored to detect early suboptimal response and then promptly escalated (**Case 4-1**). Such an approach is, however, inadequate in patients with aggressive MS, who have a much narrower treatment window and may lose precious biological time and opportunity to control their disease. In this context, it is important to tailor initial therapies to maximize efficacy, trading off any higher treatment-related risks in exchange for rapid disease control.

An induction approach has been considered and used for many years in patients deemed to have more aggressive forms of MS, especially when first seen (**Case 4-2**). This "hit hard and early" approach involves more potent agents early on in the disease course but also has the potential for more serious side effects.[95] It could be used in a temporary fashion for a limited period of time (mitoxantrone, cladribine, or cyclophosphamide) or as a more definitive therapy (alemtuzumab or autologous hematopoietic stem cell transplantation). The duration of the induction treatment is often dictated by specific toxicities, in part because of cumulative doses, and the intended choice of an "exit strategy" (what to do following induction). Therapeutic response needs to be monitored closely in both treatment paradigms to capture partial and nonresponders in a timely manner.

"No evidence of disease activity" (NEDA) is a new concept of disease control that should ultimately be the goal of all disease-modifying therapy.[96] It is also referred to as freedom from disease activity and is a composite of freedom from relapses and disability worsening as well as lack of MRI activity (new/enlarging T2 lesions or gadolinium-enhancing lesions). Several caveats exist concerning this concept,

Case 4-1

A 26-year-old man was diagnosed with relapsing-remitting multiple sclerosis when he presented 3 years ago with diplopia and ataxia. He initially started interferon beta-1a but developed two mild attacks in 12 months (right optic neuritis and left hand numbness), each resolving on its own. His follow-up MRI showed two new T2 lesions, and he was switched to fingolimod. In the past year, he had two additional relapses: a thoracic myelitis (T6 sensory level, mild spasticity, moderate left ankle dorsiflexor weakness, and loss of vibration in the left foot) and a brainstem attack (right internuclear ophthalmoplegia, facial myokymia, and vertigo). Both attacks were deemed moderate in severity and impacted his daily functioning; they were treated with steroids. He made a good recovery but had residual left leg fatigability and a neurogenic bladder. His Expanded Disability Status Scale (EDSS) score was 2.5. Repeat imaging 10 months after starting fingolimod demonstrated multiple gadolinium-enhancing lesions both in the brain and cervical spine (**Figure 4-1**). His disease was deemed aggressive, so he was started on alemtuzumab.

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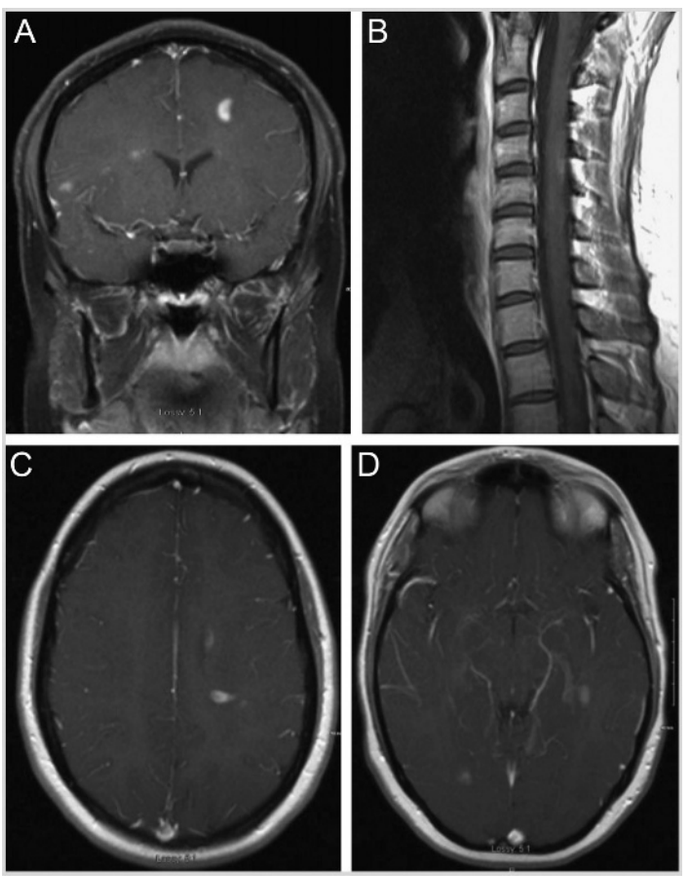

FIGURE 4-1 Follow-up brain and spinal cord MRI of the patient in **Case 4-1** showing multiple gadolinium-enhancing lesions. *A*, Coronal T1 postcontrast brain image; *B*, sagittal T1 postcontrast cervical spine image; *C*, *D*, axial postcontrast T1 brain images at different levels.

Comment. This case highlights the importance of close follow-up of both clinical and MRI status while initiating a first-line treatment. The quick emergence of disease while on first-line treatment is a telltale sign of active disease warranting treatment escalation. The continued activity with residual deficits while on an escalated therapy put his disease into the aggressive level.

but in relapsing MS, many early patients achieve NEDA when given no treatment (ie, in the placebo group of trials). This would not be the case at all with aggressive MS, a patient group highly likely to demonstrate damaging disease activity in the absence of definitive treatment. Therefore, achieving a result as close as possible to NEDA would be even more relevant in aggressive MS and should be a realistic goal for this patient group.

Aggressive Multiple Sclerosis Treatment Algorithm

Treatment algorithms for aggressive MS do not currently exist. The authors

Case 4-2

A 29-year-old woman presented for a neurologic consultation because of a 5-year history of neurologic symptoms. Five years previously, she developed right arm and hand weakness with Lhermitte phenomenon and was diagnosed by her primary physician with a cervical radiculopathy, which was treated with physical therapy and resolved. However, 1 year later, she developed a tight and squeezing sensation in her chest radiating to her back at the bra line along with numbness in her feet and urinary urgency, but this was attributed to anxiety. For the past year she has noted blurred vision in the right eye when overheated or tired, as well as severe fatigue. One month prior to her visit, she developed dysarthria, vertigo, and ataxia that was accompanied by a spastic paraparesis to the point of needing a cane to ambulate.

Her examination showed a visual acuity of 20/20 in the left eye and 20/40 in the right eye with a right afferent pupillary defect and a pale right optic disk. Her left corneal reflex was diminished, and she had left facial hypoesthesia in the V1 and V2 dermatomes. She had moderate leg spasticity with bilateral clonus and diffuse hyperreflexia. Finger extensors, hip flexors, and knee flexors were graded 4/5 bilaterally in strength, and she had moderate bilateral lower limb dysmetria. She had loss of vibration and graphesthesia in the left hand with severe sensory ataxia in the upper limbs. Her Expanded Disability Status Scale (EDSS) score was 6.0. MRI of the brain and spinal cord revealed evidence for widespread demyelination with lesions both supratentorially and infratentorially as well as in her spinal cord at C2, C5, T4, and T11 (**Figure 4-2**).

Because of her delayed diagnosis and accrued disability, IV cladribine was given initially and the possibility of autologous hematopoietic stem cell transplantation was discussed. She chose to complete a 2-year course of IV cladribine, with disease stabilization and no complications and dramatically recovered. Glatiramer acetate was initiated 6 months after finishing the cladribine induction as maintenance treatment. Four years after the diagnosis of aggressive multiple sclerosis and 2.5 years after completing the cladribine course, she remained relapse free, and her EDSS score had improved to 3.0.

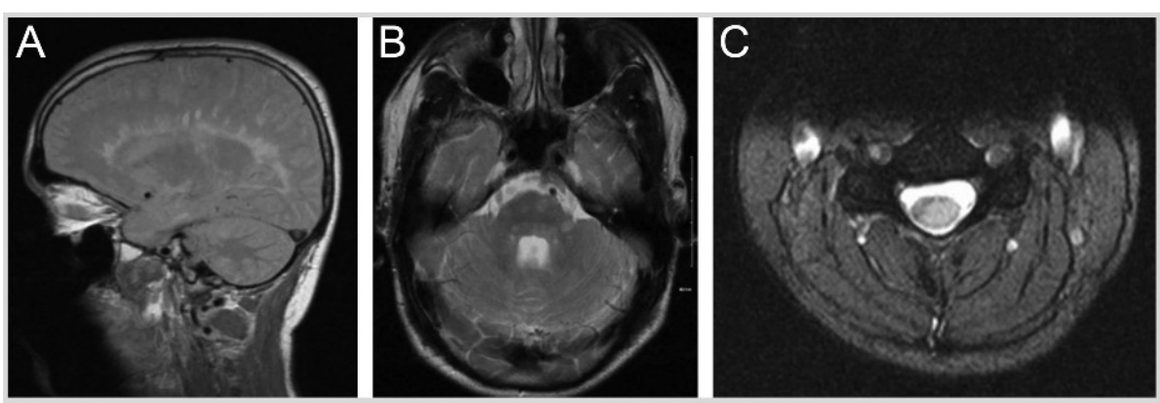

FIGURE 4-2 A high T2 lesion burden. *A*, Sagittal T2 brain MRI showing typical Dawson fingers and corpus callosum involvement; *B*, axial T2 brain MRI revealing multiple infratentorial lesions; *C*, axial T2 cervical spinal cord MRI with a large lesion involving most of the cord width.

Comment. This case is an example of recognizing aggressive disease from the beginning and moving to an induction approach for a naïve patient who had accumulated significant disability with a number of severe early attacks. It was deemed that first- or even second-line agents available at the time (natalizumab or fingolimod) would have most likely been inadequate, with additional concerns regarding the possibility of severe rebound disease should they be discontinued abruptly. Her delayed diagnosis, rapid accumulation of deficits, and MRI burden all indicated a rapidly advancing severe condition with a narrow therapeutic window of opportunity for treatment. Autologous hematopoietic stem cell transplantation would have also been an option in selected naïve cases in centers with experience in autologous hematopoietic stem cell transplantation.

propose a potential model specifically tailored for this type of patient; however, no optimal strategy exists for the sequencing of these therapies. Moreover, not all therapies will be considered, depending on familiarity, availability, experience, and proper support from colleagues in hematology/oncology who use these agents and treatments regularly (**Figure 4-3**[97]). Access, coverage, and regulatory guidelines for different agents used in the treatment of MS vary greatly around the world and even regionally within a country. Interestingly, infrastructure, local resources, expertise, and logistics of implementation of such drugs can also be very heterogeneous, mandating changes and adaptations to existing protocols.

Alemtuzumab would be the authors' first choice in patients with aggressive MS who continue to exhibit disease activity after at least 1 year of attempted treatment and failure with one or more agents, because of its proven efficacy and manageable safety issues. In this algorithm, if alemtuzumab maintains good control over the 2 years of its treatment course, then the authors would recommend it be used intermittently thereafter (yearly treatment course consisting of three doses similar to the year 2 therapy) should NEDA not be attainable. Typically, one would consider a course of alemtuzumab to

KEY POINT

- The availability, expertise, and logistics of implementation for different therapies used for multiple sclerosis vary around the world.

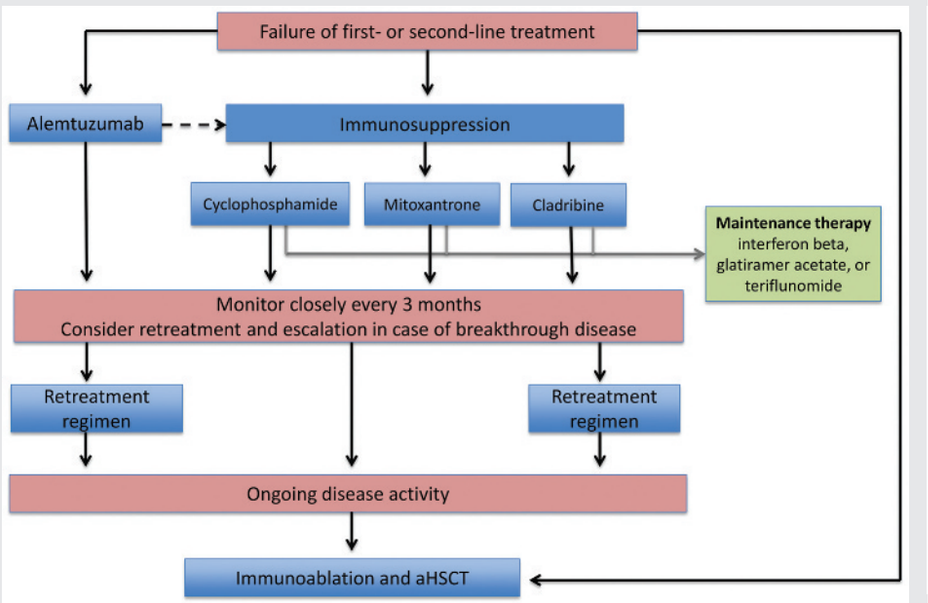

FIGURE 4-3 Proposed treatment algorithm for aggressive multiple sclerosis (MS). To meet the authors' definition of aggressive MS, patients will either not have responded to one or more therapies for up to 1 year or present naïve to treatment with many of the characteristics described in **Table 4-1**. Some of these patients might warrant induction therapy with autologous hematopoietic stem cell transplantation (aHSCT), whereas others are better suited to escalation using alemtuzumab or available immunosuppressive agents (cyclophosphamide, mitoxantrone, or cladribine). If disease activity returns after a period of success with alemtuzumab or the immunosuppressants, these agents can be used again, assuming that lifetime cumulative toxicity limits have not been reached (**Table 4-2**). Maintenance therapy with first-line agents (such as interferon beta) might also be beneficial. If MS remains refractory, we recommend moving quickly to aHSCT where possible. Patients should be assessed clinically every 3 months and radiologically every 6 months, permitting only minimal evidence of continued disease activity before considering further treatment escalation.

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KEY POINT

- It is important to keep in mind that the safety of immunosuppressant use following many of the current disease-modifying therapies, especially agents such as natalizumab, has not been established.

be the 2-year treatment (eight doses); however, if alemtuzumab fails to adequately control aggressive disease within the first year, then the authors would suggest moving quickly to autologous hematopoietic stem cell transplantation, where expertise is available. It is uncertain if the use of cladribine, cyclophosphamide, or mitoxantrone after alemtuzumab failure would be of additional benefit. In theory, they could be valid options in instances where autologous hematopoietic stem cell transplantation is not available.

In cases where alemtuzumab is not available, any of the immunosuppressive agents (cladribine, cyclophosphamide, or mitoxantrone) would be the first logical alternative consideration in the therapeutic algorithm. Patients may either stabilize or continue having suboptimal response (lack of NEDA), and if it is deemed to be refractory disease, further courses of immunosuppression could be attempted, keeping in mind the limits for some of these agents in terms of lifetime cumulative doses and the risk of toxicity. It is important to keep in mind that the safety of immunosuppressant use following many of the current disease-modifying therapies, especially agents such as natalizumab, has not been established.

Fortunately, stabilization occurs in many patients after use of the immunosuppressant agents and in approximately 70% of patients after one treatment course of alemtuzumab. However, in most cases, the control is not indefinite and maintenance treatment should be considered. Some evidence exists that patients respond well to immunomodulating agents such as interferon beta or glatiramer acetate in this postimmunosuppression setting and there do not appear to be any additive or sequential toxicities. The safety and efficacy of maintenance therapy using newer agents postimmunosuppression is not established.

For some agents, notably alemtuzumab or cladribine, an alternative option exists instead of choosing a typical first-line agent for maintenance. If, after a period of clinical stability, disease activity reappears, either alemtuzumab or cladribine could be used again (a 3-day course of alemtuzumab or 4-day cycle of cladribine every 6 months for 2 cycles) in a given year. If breakthrough disease occurs following cyclophosphamide or mitoxantrone, assuming lifetime cumulative toxicity limits have not been reached, these agents could be used again. If limits have been reached, the logical next step would be to proceed to alemtuzumab, cladribine, or even autologous hematopoietic stem cell transplantation.

Severe disease seems to be unstoppable in certain patients who continue to have relapses, MRI activity, and unrelenting progression and who ultimately fail more potent agents over the years. For individuals who have accrued significant disability and treatment-related toxicities with no evidence of further relapse or MRI lesion development over at least 2 years, further immune suppression may not be warranted.

However, for some young patients or individuals who are still within their personal "therapeutic window" (ie, evidence of active inflammatory disease), autologous hematopoietic stem cell transplantation may be an alternative in centers where autologous hematopoietic stem cell transplantation expertise is available.

In assessing the response to treatment for aggressive MS, the authors recommend lowering the acceptable threshold for continued disease activity. Diligent monitoring is critical to capture suboptimal response in a timely manner and intercede with a more

effective strategy. Whereas some physicians might be willing to accept minimal evidence of disease activity, such as a mild relapse or a couple of new MRI lesions in routine relapsing disease, these would be unacceptable in a case of aggressive MS along with any indication of EDSS score progression. Any evidence of continued disease activity should be reason enough to worry about the success of the treatment chosen for aggressive MS.

Personalizing the Treatment for Aggressive Multiple Sclerosis

It is important to consider not only the factors that might predispose to a better response using the aggressive MS strategy the authors propose, but also other patient characteristics, including the desire for pregnancy, comorbidities, previous use of immunosuppressants, JC virus seropositivity, geographic parameters, health insurance coverage, and personal preference (of both patient and treating neurologist), to determine the treatment selection. Risk tolerance differs significantly between patients with MS and their neurologists. Some studies have shown that patients with MS are willing to take more risks than their treating neurologists; this may be related to their worse perception of their own disease.[98,99] Risk-averse patients are more likely to choose less effective drugs with a safer side effect profile, whereas risk-tolerant patients will accept higher risks if the benefit of higher efficacy is warranted. It is important to have a good discussion with patients and their families in order for all to understand the gravity of the condition (aggressive MS) and the planned treatment strategy to better ensure proper follow-up, not only for monitoring the success of the planned strategy, but also to mitigate against some of the potential risks due to the choice of treatment.

CONCLUSION

Early identification of patients with aggressive MS is critical since they are at higher risk of early progression and tend to have disease that is refractory to control using conventional disease-modifying therapies. Opportune and tailored implementation of treatment strategies specific to this set of patients may have a positive impact on disease severity and neurologic disability. The use of more aggressive treatment agents will require ongoing safety surveillance to mitigate possible known and unknown risks. So much could be gained from an organized clinical trial for treating aggressive MS, but such a study would be ethically challenging since a placebo cannot be used and most disease-modifying therapies are unlikely to be of benefit. Perhaps with a more uniform definition of aggressive MS and the treatment approach the authors propose here, data can be compiled from small single-center studies over time to determine which treatment regimen of those suggested might offer superior benefit and safety.

KEY POINTS

- Risk tolerance and risk aversion differ from patient to patient and between patients and treating neurologists, dictating the degree of the aggressive or intensive treatment plan.
- Early detection and treatment of aggressive multiple sclerosis is crucial to prevent irreversible damage and disability.
- Identification of suboptimal response is also paramount to redirect treatment if breakthrough disease is ongoing despite more potent agents in view of the complexity of the new agents and unknown long-term safety profile.

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