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High-dose chemotherapy and multiple sclerosis

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Abstract

Purpose of review—Immunomodulatory medications for multiple sclerosis provide only modest control of this potentially debilitating auto-immune disease of the central nervous system. The immunosuppression provided by high-dose chemotherapy has been studied to address treatment-refractory disease. In this review, we discuss the recent significant work in this field and its associated controversies.

Recent findings—Conclusive evidence for the efficacy of high-dose chemotherapy with stem cell rescue is lacking given the lack of uniform patient populations and varying treatment protocols. Moreover, the significant toxicity associated with this procedure has dampened enthusiasm for its widespread use. High-dose chemotherapy without stem cell rescue has been trialed as a less toxic approach that eliminates the possibility of re-infusing autoreactive lymphocytes found in the stem cell product.

Summary—Before high-dose chemotherapy with or without stem cell rescue can be adopted for clinical practice, both approaches require testing in randomized clinical trials. Both procedures have the possibility of decreasing disease activity but high-dose chemotherapy without stem cell rescue having a more favorable safety profile, may prove a more significant advance in the field of high-dose therapy for multiple sclerosis.

Keywords

autologous stem cell transplantation; high-dose cyclophosphamide; multiple sclerosis

Introduction

Multiple sclerosis (MS), an auto-immune disorder, results in inflammatory and degenerative pathology in the brain, spinal cord, and optic nerves. Relapsing–remitting MS (RRMS) manifests clinically with sporadic episodes of neurologic symptoms, whereas secondary (SPMS) and primary progressive MS result in accrual of disability without clear relapses

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[1]. Therapeutic response is assessed by evaluation of rates of clinical relapse and disability accrual, and measurement of lesion burden with brain magnetic resonance imaging [2].

The standard MS therapies are disease modifying agents aimed at blunting the auto-immune response without producing significant immune suppression. Interferon-beta and glatiramer acetate, chronic injection therapies, have been available for almost two decades. These medications reduce the rate of relapse by approximately one-third, reduce the accrual of CNS lesion burden, and slow the accumulation of disability [3–5]. Recently, natalizumab, a monoclonal antibody against α-4 integrin, in RRMS has reduced relapses by 68% [6] but is associated with risks, such as progressive multifocal leukoencephalopathy [7•].

Because of the modest efficacy of current disease-modifying therapies for RRMS and their complete lack of efficacy in progressive MS [8•], more aggressive therapeutic options have been investigated. On the basis of their immunosuppressive properties, chemotherapeutics such as mitoxantrone and cyclophosphamide have been explored [9–12]. Although mitoxantrone is an effective remittive agent in steroid and interferon refractory MS, long-term toxicity concerns limit its use [10,13].

Inspired by the safety of high-dose chemotherapy with stem cell rescue in refractory B-cell and T-cell malignancies, this procedure has recently been studied in refractory auto-immune illnesses. Although myeloablative therapy is proven effective with an acceptable toxicity profile in hematologic malignancies [14], the toxicity of this procedure in auto-immune illness is not established, nor has its efficacy been compared to nonmyeloablative high-dose therapy. Here we review high-dose chemotherapy with and without stem cell rescue in the treatment of aggressive MS.

High-dose chemotherapy with stem cell rescue in multiple sclerosis

In 1995, Karussis *et al*. [15], based on a systemic lupus erythematosus mouse model surmised: high-dose immunosuppression followed by autologous transplantation may represent a new therapeutic approach for drug-resistant auto-immune diseases. In 1997, Fassas *et al*. [16] reported the first autologous bone marrow transplant experience in 15 MS patients. Stem cells were collected by apheresis after a cyclophosphamide/growth factor mobilization strategy. A standard carmustine/etoposide/cytarabine/melphalan (BEAM) preparative regimen was followed by stem cell infusion; rabbit antithymocyte globulin (ATG) was utilized (days +1 and +2) for in-vivo lymphocyte depletion. At 6 months follow-up, a durable neurologic improvement was described in seven patients and the era of high-dose therapy with stem cell rescue for MS began.

Since, more than 400 transplants for MS have been performed [17•,18,19•]. Given the relatively small and diverse patient populations studied, the diverse conditioning regimens utilized, and the possibility for auto-graft T-cell depletion (TCD), trial comparisons are difficult [18,19•].

Toxicity of stem cell collection

Autologous peripheral blood progenitor collection (PBPC) in hemato-oncologic diseases is safe. In a recent PBPC report, during 136 collections only three transient reactions occurred: mild hypocalcemia twice and hypotensive reaction once [20•]. However, the toxicity profile of stem cell mobilization differs in auto-immune patients. Even in the nontransplant setting, the rapid increase in polymorphonuclear leukocytes induced by granulocyte colony stimulating factors in neutropenic-auto-immune patients can lead to central nervous system disease exacerbations [21]. During a filgrastim dose-escalation stem cell mobilization study in rheumatoid patients, disease exacerbations were common [22]. As MS exacerbations also commonly occur during stem cell mobilization [23•,24–26], many current MS mobilization strategies include immunosuppression, such as 1 mg/kg methylprednisolone, concurrent with filgrastim to avoid this cytokine release syndrome [17•,25].

Toxicity of the preparative regimen and T-cell depletion

The preparative regimens used for autologous bone marrow transplant for hemato-oncologic diseases are safe. In a recent study of lymphoma patients, the treatment-related mortality (TRM) using a carmustine/etoposide/cytarabine/cyclophosphamide (BEAC) or BEAM preparative regimen was approximately 2% [27•]. However, given the early relapse rate of autologous transplantation in auto-immune illness by either autoreactive lymphocytes surviving the conditioning regimen or contaminating the graft [28], TCD has been incorporated into nearly all MS transplant trials. In the first MS trial, ATG (2.5–5.0 mg/kg, days +1 and +2) resulted in severe allergic reactions prompting methylprednisolone co-administration with ATG. Additionally, prophylactic IVIg was utilized to prevent infections [16]. As a result of severe viral and fungal infections, the development of other auto-immune illness, post-transplant lymphoproliferative disorder and death, ex-vivo–in-vivo TCD combination MS trials [29–31] have been largely abandoned.

Importantly, the increased treatment-related toxicity observed in MS patients is not limited to ATG infusion reactions and ex-vivo TCD: the increased use of steroids and in-vivo TCD both increase the treatment-related morbidity and mortality. Openshaw *et al*. [32] reported three deaths in five MS patients from influenza A, *Staphylococcus* sepsis and pneumococcal pneumonia after a busulfan/cyclophosphamide/ATG preparative regimen. In comparative analysis in 2006, the European Blood and Marrow Transplantation Group reported an overall TRM of 5.3% and a 0% TRM when limiting analysis to a BEAM/ATG preparative regimen without in-vitro purging [24]. However, they also documented an additional 4.7% death rate from MS disease progression [24]. Arguably, as the leading cause of death in MS is infectious, a 4.7% death rate requires further analysis. More recently, Hamerschlak *et al*. [17•], when comparing the same BEAM/ATG preparative regimen versus the nonmyeloablative cyclophosphamide/ATG preparative regimen, in MS patients, reported a 14.3% TRM (three deaths in 21 patients) and an overall higher statistically significant toxicity profile in the BEAM/ATG arm. To reduce the toxicity of myeloablation, a nonmyeloablative preparative regimen of high-dose cyclophosphamide and either alemtuzumab or ATG followed by autologous stem cell rescue has been trialed [23•]. Although the toxicities encountered appear less intense than those of patients undergoing a

fully ablative preparative regimen [33•], as in the early intensive TCD strategies, other autoimmune phenomenon developed [23•].

Efficacy of high-dose chemotherapy with stem cell rescue

Because of the lack of randomized controlled studies performed to date, a clear determination of the relative efficacy of stem cell transplantation strategies is difficult. Additionally, pooling of data from multiple studies into meta-analyses to overcome small sample sizes is fraught with difficulty, given the heterogeneity between studies in the mobilization and transplantation regimens used and marked differences in enrollment criteria. This understood, many of the pivotal studies with this approach report clinical efficacy that warrants attention. Fassas *et al*. [30] were the first to report efficacy data in a comprehensive study of high-dose chemotherapy with stem cell rescue (described above). This study only enrolled subjects with primary or secondary progressive MS, most of whom had significant baseline disability. Disability outcomes in clinical trials in MS are based on the Kurtzke Expanded Disability Status Scale (EDSS), an ordinal scale that rates disability from 0.0 (none) to 10.0 (death), with a score of 6.0 corresponding to the need for unilateral assistance when walking [34]. The median EDSS in this study was 6.0. During a median 40-month follow-up, 18/23 (78%) of patients had either stabilization of or improvement in their EDSS score compared to baseline. Efficacy was similar in subsequent studies, including one utilizing a total body irradiation and ATG approach, and a meta-analysis of multiple differing protocols (63% progression-free survival) [24,26,29]. Although these numbers may initially appear impressive, one must note that in a large randomized study of rituximab in primary progressive MS, the treatment group achieved the same status in 69.8% of patients, which was not statistically different from placebo [35•]. Utilization of change in EDSS score as an outcome measure for such trials can be problematic, as the probability of EDSS progression over time is reduced with increasing baseline EDSS scores [36]. Because most studies have enrolled patients with median EDSS scores in the 5.0–6.5 range, it is expected that proving efficacy would be more difficult. Unfortunately, more objective measures of clinical response, such as MRI findings, were not well standardized or described in most of these studies, which could act as supportive efficacy data if it were present.

Even more impressive efficacy appears attainable with a different patient selection strategy. Saccardi *et al*. [37] reported a 95% progression-free survival more than 6 years after a cyclophosphamide and filgrastim mobilization followed by a BEAM/ATG preparative regimen. This marked difference in outcome is likely secondary to patient selection, as this study included relapsing–remitting patients (which the above studies did not) and required the presence of gadolinium-enhancing lesions on MRI at baseline. As gadolinium enhancement is a marker of an active inflammatory state within lesions, selection for this criterion enriches for a population with a more inflammatory clinical phenotype. In fact, the mean number of gadolinium-enhanced lesions pretreatment in this study was 10.8, which is markedly higher than found in a more recent clinical trial for relapsing–remitting MS [6]. In this study, inflammatory activity was reduced (only one patient had a single gadolinium-enhanced lesion in follow-up) and there was a 64% probability of relapse-free survival at 4.5 years. With this knowledge, a more recent phase I/II study using the nonmyeloablative cyclophosphamide/alemtuzumab conditioning regimen in relapsing–remitting patients was

attempted [23•]. Sixty-six percent of patients were relapse-free in the follow-up period and improvement was noted in all of the measured scales of neurologic disability. As this was not a placebo-controlled trial, however, such results need to be viewed with caution, especially given the nature of the patients enrolled. This study recruited a very clinically active population, requiring two relapses within the previous 12 months or one relapse and one later gadolinium-enhancing lesion. Due to the natural history of RRMS, enrolling patients in the midst of elevated clinical activity leads to a phenomenon of 'regression to the mean,' with a statistical tendency for even placebo-treated patients to have reductions in rates of relapse and regression of disability [38]. Additionally, alemtuzumab itself has recently been shown to have significant independent efficacy in MS [39•].

High-dose chemotherapy without stem cell rescue in multiple sclerosis

In 1996, Brodsky *et al*. [40] published on six of 10 patients with severe aplastic anemia (SAA) who at 10 years were in a complete remission after high-dose cyclophosphamide (HDC) without bone marrow transplantation. This year, the Johns Hopkins group published a more extensive report on 67 SAA patients treated with HDC confirming the efficacy of this treatment [41••]. In 2002, we published the first report of HDC without stem cell rescue for an auto-immune neurologic illness: chronic inflammatory-demyelinating polyneuropathy and updated that experience in 2005 and 2007 [42,43]. We and others have shown HDC without stem cell rescue can decrease disease activity and improve quality of life in numerous immune-mediated illnesses [44,45•,46,47]. In 2006, based on 13 patients, we published the first report showing HDC without stem cell rescue to be effective therapy in moderate to severe refractory MS [48].

HDC without stem cell rescue is an alternative to standard autologous transplantation. Cyclophosphamide's unique metabolism is responsible for its immunosuppressive yet stem cell-sparing properties. Cyclophosphamide is essentially completely inactivated by tissue ALDH1, which converts the metabolic pathway intermediate aldophosphamide to the noncytotoxic metabolite carboxyphosphamide. Because hematopoietic progenitors highly express ALDH1, hematologic recovery is complete and rapid regardless of the dose of cyclophosphamide. Conversely, committed lymphoid cells express little or no ALDH1 and are susceptible to the alkylating effects of high-dose cyclophosphamide [49•,50]. Thus HDC completely eliminates the need for stem cell collection and its inherent toxicities and also completely eliminates any possibility of re-infusing autoreactive lymphocytes as there is no stem cell rescue.

Safety of high-dose cyclophosphamide without stem cell rescue in multiple sclerosis

Two independent studies of HDC for aggressive MS are reported. In 2009, we updated our original 2006 report [48] to 15 (eight secondary progressive and seven relapsing–remitting) MS patients who underwent HDC without stem cell rescue [51••]. Their median age was 42 (range 26–58) years; all had an advanced EDSS (median 6.5); all had recent clinically significant disease activity; all had disease progression despite at least two FDA approved disease-modifying therapies. All patients were treated with cyclophosphamide, 50 mg/kg/day, based on adjusted ideal body weight, over a 4-day period. Filgrastim (without concurrent immunosuppression) was started on the 10th day and continued until the absolute

neutrophil count rose to 1.0×10^9/l for two consecutive days. The median time of absolute neutropenia was 9 (range 6–13) days. Only expected toxicities were encountered: 53% received treatment for febrile neutropenia, one patient was treated for *Escherichia coli* bacteremia and *Clostridium difficile* colitis. During a 2-year follow-up period, no deaths occurred, no patient required re-admission for treatment-related toxicities and no other auto-immune illnesses developed [51••].

In 2008, Krishnan *et al*. [52••] reported the Johns Hopkins group's experience with HDC without stem cell rescue in nine patients with gadolinium-enhancing, aggressive RRMS. Their median age was 29 (range 20–47) years, eight patients had disease progression despite previous remittive therapy and their median EDSS was 5 (range 1.5–7.0). All patients received cyclophosphamide, 50 mg/kg/day, based on ideal body weight, over a 4-day period and filgrastim (as above). All patients had full hematopoietic recovery without stem cell rescue. Two patients developed febrile neutropenia, and three had self-limited documented infections.

Efficacy of high-dose cyclophosphamide without stem cell rescue in multiple sclerosis

In our updated report of 15 patients treated with HDC without stem cell rescue, only one patient had sustained progression of disability and nine patients had a decrease in EDSS. There were also improvements noted in quality of life and urologic symptoms. During 2 years of follow-up, only four patients had disease activity requiring additional treatment. There were no significant post-treatment changes noted on MRI, although this cohort had what appeared to be minimal MRI activity at baseline (only three with baseline-enhancing lesions) [51••].

Krishnan *et al*. [52••] treated nine patients, all of which had relapsing–remitting disease. Two patients in this cohort required rescue treatment for clinical relapses, whereas the rest remained relapse-free for 2 years. Disability also improved in this study and there was a significant reduction in the number of gadolinium-enhanced lesions on post-treatment MRI.

These studies are open to similar criticisms as discussed for the high-dose therapy with stem cell rescue trials. The small number of patients treated and the open-label nature of these studies makes a true efficacy evaluation impossible. Additionally, the lack of progression in EDSS score over the follow-up period in those with SPMS may be explained by natural history alone, given the high baseline EDSS scores in the Gladstone *et al*. study. Finally, as a result of the phenomenon of 'regression to the mean' described above, the reduction in relapse risk, gadolinium-enhanced lesions, and EDSS scores in the relapsing–remitting cohort in the Krishnan *et al*. study might also be attributable to natural history and require a comparison arm to determine relative efficacy.

Conclusion

High-dose chemotherapeutic strategies with and without stem cell rescue are interesting alternatives to standard of care for aggressive MS. Although early nonrandomized reports

suggest significant clinical activity, given the natural history of this disease, the true impact of these treatments will only be elucidated by randomized trials. Moreover, high-dose therapy with stem cell rescue poses unique toxicities in MS patients: disease flares during stem cell mobilization and the lymphocyte depletion incorporated into stem cell rescue procedures greatly increase the morbidly and mortality of the procedure. Comparatively, although limited by the small numbers of MS patients thus far treated, HDC without stem cell rescue appears to have a far more acceptable safety profile without affecting efficacy.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 234).

1. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001; 50:121–127. [PubMed: 11456302]
2. Lovblad KO, Anzalone N, Dorfler A, et al. MR imaging in multiple sclerosis: review and recommendations for current practice. Am J Neuroradiol. 2010; 31:983–989. [PubMed: 20019103]
3. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I: Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology. 1993; 43:655–661. [PubMed: 8469318]
4. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995; 45:1268–1276. [PubMed: 7617181]
5. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol. 1996; 39:285–294. [PubMed: 8602746]
6. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006; 354:899–910. [PubMed: 16510744]
7 •. Clifford DB, De Luca A, Simpson DM, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Lancet Neurol. 2010; 9:438–446. [PubMed: 20298967] This paper reviews the cases of progressive multifocal leukoencephalopathy due to natalizumab that have occurred in postmarketing surveillance, demonstrating that this infectious side-effect can occur with monotherapy and that outcomes are improved with early cessation of the drug.
8 •. Hartung HP, Aktas O. Bleak prospects for primary progressive multiple sclerosis therapy: downs and downs, but a glimmer of hope. Ann Neurol. 2009; 66:429–432. [PubMed: 19847907] This letter comments on the failure of the OLYMPUS phase II/III trial of Rituximab in primary progressive MS, which is indicative of all previous trials in primary progressive disease.

9. Khan OA, Zvartau-Hind M, Caon C, et al. Effect of monthly intravenous cyclophosphamide in rapidly deteriorating multiple sclerosis patients resistant to conventional therapy. Mult Scler. 2001; 7:185–188. [PubMed: 11475443]
10. Scott LJ, Figgitt DP. Mitoxantrone: a review of its use in multiple sclerosis. CNS Drugs. 2004; 18:379–396. [PubMed: 15089110]
11. Hommes OR, Aerts F, Bahr U, et al. Cyclophosphamide levels in serum and spinal fluid of multiple sclerosis patients treated with immunosuppression. J Neurol Sci. 1983; 58:297–303. [PubMed: 6834081]
12. Weiner HL, Cohen JA. Treatment of multiple sclerosis with cyclophosphamide: critical review of clinical and immunologic effects. Mult Scler. 2002; 8:142–154. [PubMed: 11990872]
13. Le Deley MC, Suzan F, Cutuli B, et al. Anthracyclines, mitoxantrone, radio-therapy, and granulocyte colony-stimulating factor: risk factors for leukemia and myelodysplastic syndrome after breast cancer. J Clin Oncol. 2007; 25:292–300. [PubMed: 17159192]
14. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995; 333:1540–1545. [PubMed: 7477169]
15. Karussis DM, Vourka-Karussis U, Lehmann D, et al. Immunomodulation of autoimmunity in MRL/lpr mice with syngeneic bone marrow transplantation (SBMT). Clin Exp Immunol. 1995; 100:111–117. [PubMed: 7697909]
16. Fassas A, Anagnostopoulos A, Kazis A, et al. Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: first results of a pilot study. Bone Marrow Transplant. 1997; 20:631–638. [PubMed: 9383225]
17 •. Hamerschlak N, Rodrigues M, Moraes DA, et al. Brazilian experience with two conditioning regimens in patients with multiple sclerosis: BEAM/horse ATG and CY/rabbit ATG. Bone Marrow Transplant. 2010; 45:239–248. [PubMed: 19584827] This paper fails to reproduce the 0% mortality of the BEAM/ATG preparative regimen reported by the European Blood and Marrow Transplantation Group [24].
18. Blanco Y, Saiz A, Carreras E, et al. Autologous haematopoietic-stem-cell transplantation for multiple sclerosis. Lancet Neurol. 2005; 4:54–63. [PubMed: 15620857]
19 •. Mancardi G, Saccardi R. Autologous haematopoietic stem-cell transplantation in multiple sclerosis. Lancet Neurol. 2008; 7:626–636. [PubMed: 18565456] This paper supports the need for prospective, controlled studies that show clinical efficacy of high-dose therapy with stem cell rescue.
20 •. Gasova Z, Bhuiyan-Ludvikova Z, Bohmova M, et al. PBPC collections: management, techniques and risks. Transfus Apher Sci. 2010; 43:237–243. [PubMed: 20678961] This paper reports the absence of major toxicities in apheresis collection in hemato-oncologic diseases.
21. Euler HH, Harten P, Zeuner RA, et al. Recombinant human granulocyte colony stimulating factor in patients with systemic lupus erythematosus associated neutropenia and refractory infections. J Rheumatol. 1997; 24:2153–2157. [PubMed: 9375876]
22. Snowden JA, Biggs JC, Milliken ST, et al. A randomised, blinded, placebo-controlled, dose escalation study of the tolerability and efficacy of filgrastim for haemopoietic stem cell mobilisation in patients with severe active rheumatoid arthritis. Bone Marrow Transplant. 1998; 22:1035–1041. [PubMed: 9877264]
23 •. Burt RK, Loh Y, Cohen B, et al. Autologous nonmyeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase I/II study. Lancet Neurol. 2009; 8:244–253. [PubMed: 19186105] This paper reports the increase in autoimmune phenomena when intense immunosuppression is added to high-dose cyclophosphamide.
24. Saccardi R, Kozak T, Bocelli-Tyndall C, et al. Autologous stem cell transplantation for progressive multiple sclerosis: update of the European Group for Blood and Marrow Transplantation autoimmune diseases working party database. Mult Scler. 2006; 12:814–823. [PubMed: 17263012]
25. Openshaw H, Stuve O, Antel JP, et al. Multiple sclerosis flares associated with recombinant granulocyte colony-stimulating factor. Neurology. 2000; 54:2147–2150. [PubMed: 10851379]

26. Nash RA, Bowen JD, McSweeney PA, et al. High-dose immunosuppressive therapy and autologous peripheral blood stem cell transplantation for severe multiple sclerosis. Blood. 2003; 102:2364–2372. [PubMed: 12763935]

27 •. Rifkin R, Spitzer G, Orloff G, et al. Pegfilgrastim appears equivalent to daily dosing of filgrastim to treat neutropenia after autologous peripheral blood stem cell transplantation in patients with non-Hodgkin lymphoma. Clin Lymphoma, Myeloma Leuk. 2010; 10:186–191. [PubMed: 20511163] This paper documents the low toxicity of the BEAM preparative regiment in non-Hodgkin's lymphoma, when concurrent intense T-cell deletion is not employed, in comparison to Hamerschlak *et al*. [17•].

28. Euler HH, Marmont AM, Bacigalupo A, et al. Early recurrence or persistence of autoimmune diseases after unmanipulated autologous stem cell transplantation. Blood. 1996; 88:3621–3625. [PubMed: 8896432]

29. Ni XS, Ouyang J, Zhu WH, et al. Autologous hematopoietic stem cell transplantation for progressive multiple sclerosis: report of efficacy and safety at three years of follow-up in 21 patients. Clin Transplant. 2006; 20:485–489. [PubMed: 16842526]

30. Fassas A, Anagnostopoulos A, Kazis A, et al. Autologous stem cell transplantation in progressive multiple sclerosis: an interim analysis of efficacy. J Clin Immunol. 2000; 20:24–30. [PubMed: 10798604]

31. Samijn JP, te Boekhorst PA, Mondria T, et al. Intense T cell depletion followed by autologous bone marrow transplantation for severe multiple sclerosis. J Neurol Neurosurg Psychiatry. 2006; 77:46–50. [PubMed: 16361591]

32. Openshaw H, Lund BT, Kashyap A, et al. Peripheral blood stem cell transplantation in multiple sclerosis with busulfan and cyclophosphamide conditioning: report of toxicity and immunological monitoring. Biol Blood Marrow Transplant. 2000; 6(5A):563–575. [PubMed: 11071262]

33 •. Mancardi G. Further data on autologous haemopoietic stem cell transplantation in multiple sclerosis. Lancet Neurol. 2009; 8:219–221. [PubMed: 19186106] The letter reflects the growing concern of the toxicities of ablative preparative regimes in the treatment of MS.

34. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983; 33:1444–1452. [PubMed: 6685237]

35 •. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol. 2009; 66:460–471. [PubMed: 19847908] This 96-week clinical trial of rituximab in primary progressive MS showed a 22% reduction in the rate of disability progression, but this was not statistically significant from placebo.

36. Daumer M, Griffith LM, Meister W, et al. Survival, and time to an advanced disease state or progression, of untreated patients with moderately severe multiple sclerosis in a multicenter observational database: relevance for design of a clinical trial for high dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation. Mult Scler. 2006; 12:174–179. [PubMed: 16629420]

37. Saccardi R, Mancardi GL, Solari A, et al. Autologous HSCT for severe progressive multiple sclerosis in a multicenter trial: impact on disease activity and quality of life. Blood. 2005; 105:2601–2607. [PubMed: 15546956]

38. Martinez-Yelamos S, Martinez-Yelamos A, Martin Ozaeta G, et al. Regression to the mean in multiple sclerosis. Mult Scler. 2006; 12:826–829. [PubMed: 17263014]

39 •. Coles AJ, Compston DA, Selmaj KW, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med. 2008; 359:1786–1801. [PubMed: 18946064] This phase II clinical trial of alemtuzumab versus interferon beta-1a in 334 relapsing remitting MS patients demonstrated relative superiority of alemtuzumab in reducing relapse rate and the rate of accumulation of disability but some serious auto-immune side-effects occurred in the alemtuzumab group.

40. Brodsky RA, Sensenbrenner LL, Jones RJ. Complete remission in severe aplastic anemia after high-dose cyclophosphamide without bone marrow transplantation. Blood. 1996; 87:491–494. [PubMed: 8555470]

41 ••. Brodsky RA, Chen AR, Dorr D, et al. High-dose cyclophosphamide for severe aplastic anemia: long-term follow-up. Blood. 2010; 115:2136–2141. [PubMed: 20018919] The paper reports the

long-term follow-up on the utility of high-dose cyclophosphamide without stem cell rescue in the treatment of auto-immune illnesses.

42. Gladstone DE, Prestrud AA, Brannagan TH 3rd. High-dose cyclophosphamide results in long-term disease remission with restoration of a normal quality of life in patients with severe refractory chronic inflammatory demyelinating polyneuropathy. J Peripher Nerv Syst. 2005; 10:11–16. [PubMed: 15703014]
43. Brannagan TH 3rd, Pradhan A, Heiman-Patterson T, et al. High-dose cyclophosphamide without stem-cell rescue for refractory CIDP. Neurology. 2002; 58:1856–1858. [PubMed: 12084892]
44. Brodsky RA. High dose cyclophosphamide treatment for autoimmune disorders. Sci World J. 2002; 2:1808–1815.
45 •. Petri M, Brodsky RA, Jones RJ, et al. High-dose cyclophosphamide versus monthly intravenous cyclophosphamide for systemic lupus erythematosus: a prospective randomized trial. Arthr Rheumat. 2010; 62:1487–1493. [PubMed: 20131296] This paper adds to the literature on the efficacy of high-dose cyclophosphamide to treat auto-immune illnesses.
46. Drachman DB, Adams RN, Hu R, et al. Rebooting the immune system with high-dose cyclophosphamide for treatment of refractory myasthenia gravis. Ann N Y Acad Sci. 2008; 1132:305–314. [PubMed: 18567882]
47. Gladstone DE, Prestrud AA, Brannagan TH 3rd, et al. High-dose cyclophosphamide for severe, refractory myasthenia gravis. J Neurol Neurosurg Psychiatry. 2004; 75:789–791. [PubMed: 15090586]
48. Gladstone DE, Zamkoff KW, Krupp L, et al. High-dose cyclophosphamide for moderate to severe refractory multiple sclerosis. Arch Neurol. 2006; 63:1388–1393. [PubMed: 16908728]
49 •. Emadi A, Jones RJ, Brodsky RA. Cyclophosphamide and cancer: golden anniversary. Nat Rev. 2009; 6:638–647. This is an excellent review on the cyclophosphamide's unique pharmacology.
50. Gladstone DE, Golightly MG, Brannagan TH 3rd. High dose cyclophosphamide preferentially targets naive T (CD45/CD4/RA+) cells in CIDP and MS patients. J Neuroimmunol. 2007; 190:121–126. [PubMed: 17854912]
51 ••. Gladstone DE. High dose cyclophosphamide for moderate to severe refractory multiple sclerosis: 2-year follow-up (investigational new drug No. 65863). Am J Ther. 2009 [Epub ahead of print]. This is an update of the first report of high-dose cyclophosphamide without stem cell rescue in the treatment of severe, refractory RRMS and SPMS.
52 ••. Krishnan C, Kaplin AI, Brodsky RA, et al. Reduction of disease activity and disability with high-dose cyclophosphamide in patients with aggressive multiple sclerosis. Arch Neurol. 2008; 65:1044–1051. [PubMed: 18541787] This is one of two reports of high-dose cyclophosphamide without stem cell rescue and MS.