J Neurol Neurosurg Psychiatry. 2014 Feb 19. doi: 10.1136/jnnp-2013-307207. [Epub ahead of print]

Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience.

Burman J[1], Iacobaeus E, Svenningsson A, Lycke J, Gunnarsson M, Nilsson P, Vrethem M, Fredrikson S, Martin C, Sandstedt A, Uggla B, Lenhoff S, Johansson JE, Isaksson C, Hägglund H, Carlson K, Fagius J.

Author information

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Abstract

BACKGROUND:

Autologous haematopoietic stem cell transplantation (HSCT) is a viable option for treatment of aggressive multiple sclerosis (MS). No randomised controlled trial has been performed, and thus, experiences from systematic and sustained follow-up of treated patients constitute important information about safety and efficacy. In this observational study, we describe the characteristics and outcome of the Swedish patients treated with HSCT for MS.

METHODS:

Neurologists from the major hospitals in Sweden filled out a follow-up form with prospectively collected data. Fifty-two patients were identified in total; 48 were included in the study and evaluated for safety and side effects; 41 patients had at least 1 year of follow-up and were further analysed for clinical and radiological outcome. In this cohort, 34 patients (83%) had relapsing-remitting MS, and mean follow-up time was 47 months.

RESULTS:

At 5 years, relapse-free survival was 87%; MRI event-free survival 85%; expanded disability status scale (EDSS) score progression-free survival 77%; and disease-free survival (no relapses, no new MRI lesions and no EDSS progression) 68%. Presence of gadolinium-enhancing lesions prior to HSCT was associated with a favourable outcome (disease-free survival 79% vs 46%, p=0.028). There was no mortality. The most common long-term side effects were herpes zoster reactivation (15%) and thyroid disease (8.4%).

CONCLUSIONS:

HSCT is a very effective treatment of inflammatory active MS and can be performed with a high degree of safety at experienced centres.

Am J Stem Cells. 2013 Jun 30;2(2):95-107. Print 2013.

The development of hematopoietic and mesenchymal stem cell transplantation as an effective treatment for multiple sclerosis.

Holloman JP, Ho CC, Hukki A, Huntley JL, Gallicano GI.

Source

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Abstract

This article examines the current use and future implications of stem cell therapy in treating Multiple Sclerosis (MS). MS is the most common neurological disease in young adults, affecting approximately two million people worldwide. Currently there is no cure for MS. The standard treatment of MS involves disease-modifying drugs, which work to alleviate the symptoms of MS. However, these drugs carry adverse side effects and are ineffective in preventing disease progression in many MS patients. Hematopoietic stem cell transplantation (HSCT) was first used in 1995 to treat patients with severe rapidly progressing MS. The HSCT treatment protocol has evolved into a less intense conditioning regimen that is currently demonstrating efficacy in treating patients with variable disease severity-with best results in early-stage rapidly progressing MS patients with active CNS inflammation. Mesenchymal stem cell therapy (MSCT) is an experimental stem cell therapy currently undergoing clinical trials. Animal models and early clinical trials have shown promise that MSCT might be a low risk treatment to precipitate neuroregeneration and immunomodulation in MS patients. Specifically, neuroprogenitor and placental-derived mesenchymal stem cells offer the best hope for a practical treatment for MS. Stem cell therapy, and perhaps a combinatorial therapeutic approach, holds promise for a better treatment for MS.

Immunology. 2013 May 30. doi: 10.1111/imm.12129. [Epub ahead of print]

T cell responses after hematopoietic stem cell transplantation for aggressive relapsing-remitting multiple sclerosis.

Burman J, Fransson M, Tötterman TH, Fagius J, Mangsbo SM, Loskog AS.

Source

Department of Neurosciences, Uppsala University, Uppsala, Sweden; Department of Neurology, Uppsala University Hospital, Uppsala, Sweden; Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, Uppsala, Sweden.

Abstract

Autologous hematopoietic stem cell transplantation (HSCT) for relapsing-remitting multiple sclerosis is a potentially curative treatment, which can give rise to long-term disease remission. However, the mode of action is not yet fully understood. The aim of the study was to evaluate similarities and differences of the CD4+ T cell populations between HSCT-treated patients (n=12) and healthy controls (n=9). More specifically, we performed phenotyping of memory T cells, Tregs, T helper type 1 (Th1) and T helper type 17 (Th17) cells. Further, T cell reactivity to a tentative antigen: myelin oligodendrocyte glycoprotein was investigated in these patient populations. Patients treated with natalizumab (n=15) were included as a comparative group. White blood cells were analyzed with flow cytometry and T cell culture supernatants were analyzed with magnetic bead panel immunoassays. HSCT-treated patients had similar levels of Tregs, Th1 and Th17 cells as healthy subjects, whereas natalizumab-treated patients had lower frequencies of Tregs, and higher frequencies of Th1 and Th17 cells. Cells from HSCT-treated patients cultured with overlapping peptides from myelin oligodendrocyte glycoprotein produced more TGF-β1 than natalizumab-treated patients suggestive of a suppressive response. Conversely, T cells from natalizumab-treated patients cultured with those peptides produced more IL-17, IL-1 and IL-10 indicating a Th17 response. In conclusion, we demonstrate circumstantial evidence for the removal of auto-reactive T cell clones as well as development of tolerance after HSCT. These results parallel the long-term disease remission seen post HSCT.

Curr Treat Options Neurol. 2013 Jun;15(3):270-80. doi: 10.1007/s11940-013-0234-9.

Autologous hematopoietic stem cell transplantation as a treatment option for aggressive multiple sclerosis.

Pfender N, Saccardi R, Martin R.

Source

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Abstract

OPINION STATEMENT:

Despite the development of several injectable or oral treatments for relapsing-remitting multiple sclerosis (RRMS), it remains difficult to treat patients with aggressive disease, and many of these continue to develop severe disability. During the last two decades autologous hematopoietic stem cell transplantation (aHSCT) has been explored with the goal to eliminate an aberrant immune system and then re-install a healthy and tolerant one from hematopoietic precursor cells that had been harvested from the patient prior to chemotherapy. Clinical studies have shown that aHSCT is able to completely halt disease activity in the majority of patients with aggressive RRMS. Research on the mechanisms of action supports that aHSCT indeed leads to renewal of a healthy immune system. Below we will summarize important aspects of aHSCT and mention the currently best-examined regimen.

Expert Rev Neurother. 2013 May;13(5):567-78. doi: 10.1586/ern.13.36.

Hematopoietic stem cell transplantation in multiple sclerosis.

Karussis D, Petrou P, Vourka-Karussis U, Kassis I.

Source

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Abstract

It is widely accepted that the main common pathogenetic pathway in multiple sclerosis (MS) involves an immune-mediated cascade initiated in the peripheral immune system and targeting CNS myelin. Logically, therefore, therapeutic approaches to the disease include modalities aiming at downregulation of the various immune elements that are involved in this immunological cascade. Since the introduction of interferons in 1993, more specific immunoactive drugs have been introduced, but still most of them can, at best, effectively modulate only the early relapsing phases of MS. The more progressed phases of the disease are not efficiently amendable by the existing immunomodulatory drugs. Moreover, localized and compartmentized inflammation in the CNS, which seems to be mostly responsible for the chronic axonal damage and resulting progression of disability, is less affected by the current drugs. A more radical approach to suppress all the inflammation in MS, including that into the CNS, could theoretically be achieved with high-dose immunosuppression using strong cytotoxic medications and resetting of the immune system by hematopoietic stem cell transplantation (HSCT). HSCT, both allogeneic and autologous, has been tried as a novel therapeutic approach in various autoimmune diseases. During the last 15 years several (mostly open) clinical studies evaluated the effect of HSTC on MS patients; the published papers showed that a high proportion of the HSCT-treated MS patients were stabilized, or even improved after the transplantation and have generally indicated a beneficial effect on disease progression. In this review, the rationale of HSCT and the summary of the results of the existing clinical trials are presented. Despite the fact that it is difficult to collectively summarize the results of all the trials, due to lack of uniformity in the conditioning and treatment protocols and of completed controlled studies, these clinical studies have provided a strong 'proof of concept' for HSCT in MS and have significantly contributed to our understanding of the advantages and disadvantages of each approach and HSCT protocol.

Neurotherapeutics. 2013 Jan;10(1):68-76. doi: 10.1007/s13311-012-0162-5.

Hematopoietic stem cell therapy for multiple sclerosis: top 10 lessons learned.

Atkins HL, Freedman MS.

Source

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Abstract

Reports from more than 600 hematopoietic stem cell transplants (HSCT) have appeared in the medical literature for the last 1 and one-half decades. The patient's own stem cells are harvested and stored temporarily while high doses of chemotherapy and biologics are used to destroy the auto-destructive immune system. The immune system is regenerated from the infused autologous hematopoietic stem cells. Increasing clinical experience has refined patient selection criteria and management in the peri-transplant period leading to a reduction in treatment-related complications. HSCT, when used to treat patients with aggressive highly active multiple sclerosis, can reduce or eliminate ongoing clinical relapses, halt further progression, and reduce the burden of disability in some patients, in the absence of chronic treatment with disease-modifying agents. The top 10 lessons learned from the growing experience using HSCT for the treatment of multiple sclerosis are discussed.

Exp Hematol. 2012 Nov;40(11):892-8. doi: 10.1016/j.exphem.2012.07.003. Epub 2012 Jul 4.

Autologous hematopoietic stem cell transplantation with reduced-intensity conditioning in multiple sclerosis.

Shevchenko JL, Kuznetsov AN, Ionova TI, Melnichenko VY, Fedorenko DA, Kartashov AV, Kurbatova KA, Gorodokin GI, Novik AA.

Source

Pirogov National Medical Surgical Center, the Department of Haematology and Cellular Therapy and the Department of Neurology, Moscow, Russia.

Abstract

High-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation (AHSCT) is a new and promising approach to multiple sclerosis (MS) treatment. In this article, we present the results of a prospective phase II open-label single-center study with the analysis of the safety and efficacy of high-dose immunosuppressive therapy+AHSCT with reduced-intensity conditioning regimen in 95 patients with different types of MS. The patients underwent early, conventional, and salvage/late transplantation. Efficacy was evaluated based on clinical and quality of life outcomes. No transplantation-related deaths were observed. The mobilization and transplantation procedures were well tolerated. All the patients, except one, responded to the treatment. At long-term follow-up (mean 46 months), the overall clinical response in terms of disease improvement or stabilization was 80%. The estimated progression-free survival at 5 years was 92% in the group after early AHSCT vs 73% in the group after conventional/salvage AHSCT. Statistically significant difference between the survival probabilities of two groups was determined ($p = 0.01$). No active, new, or enlarging lesions in magnetic resonance imaging were registered in patients without disease progression. All patients who did not have disease progression were off therapy throughout the post-transplantation period. AHSCT was accompanied by a significant improvement in patient's quality of life with statistically significant changes in the majority of quality of life parameters ($p < 0.05$).The results of our study support the feasibility of AHSCT with reduced-intensity conditioning in MS patients. Multicenter cooperative studies are needed for better assessment of treatment results and optimization of the treatment protocol of AHSCT with reduced-intensity conditioning regimens in MS.

Mult Scler. 2012 Jun;18(6):825-34. doi: 10.1177/1352458512438454. Epub 2012 Mar 1.

A prospective, randomized, controlled trial of autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: a position paper.

Saccardi R, Freedman MS, Sormani MP, Atkins H, Farge D, Griffith LM, Kraft G, Mancardi GL, Nash R, Pasquini M, Martin R, Muraro PA; European Blood and Marrow Transplantation Group; Center for International Blood and Marrow Research; HSCT in MS International Study Group.

Collaborators (26)

Amato MP, Arnold DL, Atkins H, Carreras E, Chen JT, Di Gioia M, Farge D, Fassas A, Freedman MS, Griffith LM, Hutton GJ, Jacobson S, Kraft G, Mancardi GL, Martin R, Massacesi L, Muraro PA, Nash R, Pasquini M, Pavletic S, Racke MK, Saccardi R, Schippling S, Sormani MP, Storek J, Wundes A.

Source

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Abstract

BACKGROUND:

Haematopoietic stem cell transplantation (HSCT) has been tried in the last 15 years as a therapeutic option in patients with poor-prognosis autoimmune disease who do not respond to conventional treatments. Worldwide, more than 600 patients with multiple sclerosis (MS) have been treated with HSCT, most of them having been recruited in small, single-centre, phase 1-2 uncontrolled trials. Clinical and magnetic resonance imaging outcomes from case series reports or Registry-based analyses suggest that a major response is achieved in most patients; quality and duration of response are better in patients transplanted during the relapsing-remitting phase than in those in the secondary progressive stage.

OBJECTIVES:

An interdisciplinary group of neurologists and haematologists has been formed, following two international meetings supported by the European and American Blood and Marrow Transplantation Societies, for the purpose of discussing a controlled clinical trial, to be designed within the new scenarios of evolving MS treatments.

CONCLUSIONS:

Objectives of the trial, patient selection, transplant technology and outcome assessment were extensively discussed. The outcome of this process is summarized in the present paper, with the goal of establishing the background and advancing the development of a prospective, randomized, controlled multicentre trial to assess the clinical efficacy of HSCT for the treatment of highly active MS.

Comment in

- Autologous hematopoietic stem cell transplantation for multiple sclerosis--if confused or hesitant, remember: 'treat with standard immune suppressive drugs and if no inflammation, no response'. [Mult Scler. 2012]

Mult Scler. 2012 Aug;18(8):1188-92. doi: 10.1177/1352458511434067. Epub 2012 Jan 17.

No proinflammatory signature in CD34+ hematopoietic progenitor cells in multiple sclerosis patients.

Lutterotti A, Jelcić I, Schulze C, Schippling S, Breiden P, Mazzanti B, Reinhardt S, DiGioia M, Repice A, Massacesi L, Sputtek A, Salinas-Riester G, Kroeger N, Sospedra M, Saccardi R, Zander A, Martin R.

Source

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Abstract

Autologous hematopoietic stem cell transplantation (aHSCT) has been used as a therapeutic approach in multiple sclerosis (MS). However, it is still unclear if the immune system that emerges from autologous CD34+ hematopoietic progenitor cells (HPC) of MS patients is pre-conditioned to re-develop the proinflammatory phenotype. The objective of this article is to compare the whole genome gene and microRNA expression signature in CD34+ HPC of MS patients and healthy donors (HD). CD34+ HPC were isolated from peripheral blood of eight MS patients and five HD and analyzed by whole genome gene expression and microRNA expression microarray. Among the differentially expressed genes (DEGs) only TNNT1 reached statistical significance (logFC=3.1, $p<0.01$). The microRNA expression was not significantly different between MS patients and HD. We did not find significant alterations of gene expression or microRNA profiles in CD34+ HPCs of MS patients. Our results support the use of aHSCT for treatment of MS.

Biol Blood Marrow Transplant. 2012 Jan;18(1 Suppl):S177-83. doi: 10.1016/j.bbmt.2011.11.020.

Autologous hematopoietic stem cell transplantation for autoimmune disease--is it now ready for prime time?

Atkins HL, Muraro PA, van Laar JM, Pavletic SZ.

Source

The Ottawa Hospital Blood and Marrow Transplant Program and Ottawa Hospital Research Institute, Ottawa, Ontario, Canada.

Abstract

Current systemic therapies are rarely curative for patients with severe life-threatening forms of autoimmune disease (AID). During the past 15 years, autologous hematopoietic stem cell transplantation (HCT) has been demonstrated to cure some patients with severe AID refractory to all other available therapies, and thus AID has become an emerging indication for cell therapy. The sustained clinical effects after autologous HCT are better explained by qualitative change in the reconstituted immune repertoire rather than transient depletion of immune cells. Since 1996, more than 1300 AID patients have been registered by the European Group for Blood and Marrow Transplantation (EBMT) and almost 500 patients by the Center for International Blood and Marrow Transplant Research (CIBMTR). Autologous HCT is most commonly performed for patients with multiple sclerosis (MS) or systemic sclerosis (SSc). Systemic lupus, Crohn's disease, type I diabetes, and juvenile idiopathic arthritis are other common indications. Allogeneic transplants are still considered too toxic for use in AID, except for cases of immune cytopenia. Although biologic therapies have been effective at controlling the manifestations of the disease, they require continuous administration, thus raising questions about their increasing costs, morbidity, and mortality related to prolonged therapy. Perhaps it is a reasonable time to ask, "Is autologous HCT for severe AID now ready for prime time?" Yet, the paucity of controlled studies, the short-term toxicities, and the upcoming availability of second-generation biologic and targeted immunotherapies argues that perhaps HCT for AID should be still limited to clinical trials. In this article, we focus on the results of autologous HCT for MS and SSc because these are the two most commonly transplanted diseases. The promising data that is emerging may establish these diseases as standard indications for HCT.

Neurol Sci. 2012 Aug;33(4):881-6. doi: 10.1007/s10072-011-0859-y. Epub 2011 Dec 8.

Long-term efficacy of autologous haematopoietic stem cell transplantation in multiple sclerosis at a single institution in China.

Chen B, Zhou M, Ouyang J, Zhou R, Xu J, Zhang Q, Yang Y, Xu Y, Shao X, Meng L, Wang J, Xu Y, Ni X, Zhang X.

Source

Department of Hematology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, 321 Zhongshan Road, Nanjing 210008, People's Republic of China.

Abstract

Autologous haematopoietic stem cell transplantation (AHSCT) is a promising treatment for multiple sclerosis (MS) patients who have not adequately responded to conventional therapies. We retrospectively evaluated the safety and long-term clinical outcome of AHSCT in MS patients in China. Twenty-five patients with various types of MS were treated with AHSCT. Peripheral blood stem cells were derived by leukapheresis after mobilized with granulocyte colony-stimulating factor. Then CD34+ cell selection of the graft was performed and anti-thymocyte globulin was given for T-cell depletion, with the conditioning regimen BEAM adopted and early and late toxicities recorded. Long-term responses were evaluated by the expanded disability status scale (EDSS), progression-free survival and gadolinium-enhanced magnetic resonance imaging scans. 10, 7 and 8 patients experienced neurological improvement, stabilization and progression, respectively. The median EDSS scores observed over 1-year follow-up after transplantation (5.5-7.0) were consistently lower than the baseline (8.0). The progression-free survival rate was 74, 65 and 48% at 3, 6 and 9 years post-transplant. 58% cases (7/12) had active lesions at baseline and all turned to inactive status in the years of follow-up. 25% cases (3/12) experienced progression after transplantation but had no active lesions in MRI over the whole follow-up period. 17% cases (2/12) without active lesions at baseline progressed active lesions in MRI. The major early toxicity resulted in fever and late toxicity caused transplantation-related mortality due to severe pneumonia and varicella-zoster virus hepatitis, respectively. AHSCT is a feasible treatment for severe MS and its long-term efficacy is favorable.

Hematology Am Soc Hematol Educ Program. 2011;2011:280-4. doi: 10.1182/asheducation-2011.1.280.

Successes and failures of stem cell transplantation in autoimmune diseases.

Tyndall A.

Source

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Abstract

Over the past 15 years, more than 1500 patients have received HSCT, mostly autologous, as treatment for a severe autoimmune disease (AD). More than 1000 of these have been registered in the European Group for Bone Marrow Transplantation (EBMT) and European League Against Rheumatism (EULAR) combined database. A recent retrospective analysis of 900 patients showed that the majority had multiple sclerosis (MS; n = 345) followed by systemic sclerosis (SSc; n = 175), systemic lupus erythematosus (SLE; n = 85), rheumatoid arthritis (RA; n = 89), juvenile idiopathic arthritis (JIA; n = 65), and idiopathic cytopenic purpura (ITP; n = 37). An overall 85% 5-year survival and 43% progression-free survival was seen, with 100-day transplantation-related mortality (TRM) ranging between 1% (RA) and 11% (SLE and JIA). Approximately 30% of patients in all disease subgroups had a complete response, often durable despite full immune reconstitution. In many patients, such as in those with SSc, morphological improvement such as reduction of skin collagen and normalization of microvasculature was documented beyond any predicted known effects of intense immunosuppression alone. The high TRM was in part related to conditioning intensity, comorbidity, and age, but until the results of the 3 prospective randomized trials are known, an evidence-based modification of the conditioning regimen will not be possible.(1) In recent years, multipotent mesenchymal stromal cells (MSCs) have been tested in various AD, exploiting their immune-modulating properties and apparent low acute toxicity. Despite encouraging small phase 1/2 studies, no positive data from randomized, prospective studies are as yet available in the peer-reviewed literature.

PMID:

22160046

[PubMed - indexed for MEDLINE]

Free full text

Mult Scler. 2012 Jun;18(6):835-42. doi: 10.1177/1352458511429320. Epub 2011 Nov 29.

Autologous haematopoietic stem cell transplantation with an intermediate intensity conditioning regimen in multiple sclerosis: the Italian multi-centre experience.

Mancardi GL, Sormani MP, Di Gioia M, Vuolo L, Gualandi F, Amato MP, Capello E, Currò D, Uccelli A, Bertolotto A, Gasperini C, Lugaresi A, Merelli E, Meucci G, Motti L, Tola MR, Scarpini E, Repice AM, Massacesi L, Saccardi R; Italian BMT Study Group.

Collaborators (15)

Donnini I, Bosi A, Guidi S, Bagigalupo A, Bonzano L, Bruzzi P, Roccatagliata L, Antenucci R, Granella F, Martino G, Rottoli M, Solaro C, Salvi F, Barilaro A, Capobianco M.

Source

Department of Neuroscience, Ophthalmology and Genetics, University of Genoa, Genoa, Italy.

Abstract

BACKGROUND:

Over recent years numerous patients with severe forms of multiple sclerosis (MS) refractory to conventional therapies have been treated with intense immunosuppression followed by autologous haematopoietic stem cell transplantation (AHSCT). The clinical outcome and the toxicity of AHSCT can be diverse, depending on the various types of conditioning protocols and on the disease phase.

OBJECTIVES:

To report the Italian experience on all the consecutive patients with MS treated with AHSCT with an intermediate intensity conditioning regimen, named BEAM/ATG, in the period from 1996 to 2008.

METHODS:

Clinical and magnetic resonance imaging outcomes of 74 patients were collected after a median follow-up period of 48.3 (range = 0.8-126) months.

RESULTS:

Two patients (2.7%) died from transplant-related causes. After 5 years, 66% of patients remained stable or improved. Among patients with a follow-up longer than 1 year, eight out of 25 subjects with a relapsing-remitting course (31%) had a 6-12 months confirmed Expanded Disability Status Scale improvement > 1 point after AHSCT as compared with one out of 36 (3%) patients with a secondary progressive disease course (p = 0.009). Among the 18 cases with a follow-up longer than 7 years, eight (44%) remained stable or had a sustained improvement while 10 (56%), after an initial period of stabilization or improvement with median duration of 3.5 years, showed a slow disability progression.

CONCLUSIONS:

This study shows that AHSCT with a BEAM/ATG conditioning regimen has a sustained effect in suppressing disease progression in aggressive MS cases unresponsive to conventional therapies. It can also cause a sustained clinical improvement, especially if treated subjects are still in the relapsing-remitting phase of the disease.

Bone Marrow Transplant. 2012 Jul;47(7):946-51. doi: 10.1038/bmt.2011.208. Epub 2011 Nov 7.

Autologous hematopoietic cell transplantation following high-dose immunosuppressive therapy for advanced multiple sclerosis: long-term results.

Bowen JD, Kraft GH, Wundes A, Guan Q, Maravilla KR, Gooley TA, McSweeney PA, Pavletic SZ, Openshaw H, Storb R, Wener M, McLaughlin BA, Henstorf GR, Nash RA.

Source

Swedish Neuroscience Institute, Seattle, WA, USA.

Abstract

The purpose of the study was to determine the long-term safety and effectiveness of high-dose immunosuppressive therapy (HDIT) followed by autologous hematopoietic cell transplantation (AHCT) in advanced multiple sclerosis (MS). TBI, CY and antithymocyte globulin were followed by transplantation of autologous, CD34-selected PBSCs. Neurological examinations, brain magnetic resonance imaging and cerebrospinal fluid (CSF) for oligoclonal bands (OCB) were serially evaluated. Patients (n=26, mean Expanded Disability Status Scale (EDSS)=7.0, 17 secondary progressive, 8 primary progressive, 1 relapsing/remitting) were followed for a median of 48 months after HDIT followed by AHCT. The 72-month probability of worsening ≥1.0 EDSS point was 0.52 (95% confidence interval, 0.30-0.75). Five patients had an EDSS at baseline of ≤6.0; four of them had not failed treatment at last study visit. OCB in CSF persisted with minor changes in the banding pattern. Four new or enhancing lesions were seen on MRI, all within 13 months of treatment. In this population with high baseline EDSS, a significant proportion of patients with advanced MS remained stable for as long as 7 years after transplant. Non-inflammatory events may have contributed to neurological worsening after treatment. HDIT/AHCT may be more effective in patients with less advanced relapsing/remitting MS.

PMID:

22056644

[PubMed - indexed for MEDLINE]

PMCID:

PMC3276694

Free PMC Article

Neurotherapeutics. 2011 Oct;8(4):643-9. doi: 10.1007/s13311-011-0062-0.

Immune mechanisms underlying the beneficial effects of autologous hematopoietic stem cell transplantation in multiple sclerosis.

Gosselin D, Rivest S.

Source

Laboratory of Endocrinology and Genomics, CHUQ Research Center and Department of Molecular Medicine, Faculty of Medicine, Laval University, Québec G1V4G2, Canada.

Abstract

A recent phase I/II clinical trial drew serious attention to the therapeutic potential of autologous hematopoietic stem cell transplantation (AHSCT) in multiple sclerosis. However, questions were raised as to whether these beneficial effects should be attributed to the newly reconstituted immune system per se, or to the lymphoablative conditioning regimen-induced immunosuppression, given that T-cell depleting combinational drug therapies were used in the study. We discuss here the possibility that both AHSCT and T-cell depleting therapies may re-program alternatively the immune system, and why transplantation of CD34+ hematopoietic stem cells may offer AHSCT a possible advantage regarding long-term remission.

PMID:

21904792

[PubMed - indexed for MEDLINE]

PMCID:

PMC3250285

Free PMC Article

Expert Opin Biol Ther. 2011 Sep;11(9):1193-201. doi: 10.1517/14712598.2011.580272. Epub 2011 May 24.

Autologous haemopoietic stem cell transplantation for autoimmune diseases.

Zeher M, Papp G, Szodoray P.

Source

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Abstract

INTRODUCTION:

Autoimmune diseases are signified by complex errors of immune-regulation, and the development of autoreactive T and B cells targeting self-antigens, which eventually can lead to permanent organ damage. Despite novel therapeutic protocols, the disease course is chronic, debilitating and in some instances the outcome is lethal. Previously, stem cell transplantation has been reported to be beneficial in autoimmune animal models, as well as in autoimmune diseases related to hematological abnormalities, which opened potential new avenues in the treatment of human autoimmune diseases.

AREAS COVERED:

In this review, the authors describe the compound cellular regulatory effects of autologous hemopoietic stem cell transplantation (ASCT) and also clinical observations, related to the therapy in a variety of organ-specific and systemic autoimmune diseases.

EXPERT OPINION:

ASCT has a broad effect on the re-populated immune system, complex regulatory potentials and long term beneficial effect via down-regulating immune-reactivity, yet its widespread use in autoimmune diseases is limited, mostly due to the serious side-effects of the conditioning treatments. However, in certain autoimmune diseases with severe debilitating, or even life-threatening course, including systemic lupus erythematosus, systemic sclerosis or multiple sclerosis, ASCT can be a reasonable choice when conventional therapy has failed.

Curr Opin Investig Drugs. 2010 Nov;11(11):1265-75.

Resetting autoimmunity in the nervous system: The role of hematopoietic stem cell transplantation.

Muraro PA, Abrahamsson SV.

Source

Imperial College London, Centre for Neurosciences, Department of Medicine, Burlington Danes Building, Room E415, 160 Du Cane Road, London, W12 0NN, UK. p.muraro@imperial.ac.uk

Abstract

According to current concepts for multiple sclerosis (MS), a fundamental pathogenic role is played by T- and B-cells that inappropriately recognize self antigens and initiate a cell-mediated or humoral inflammatory reaction that injures myelin and axons, and results in neural dysfunction and loss. Transplantation of bone marrow-derived hematopoietic stem cells following high-dose immunosuppression is being evaluated as an experimental treatment for severe forms of immune-mediated disorders, including MS. The primary goal of this therapeutic approach is to induce medication-free remission from new disease activity by correcting the immune aberrations that promote the attack against self tissue; this approach is termed 'immune repair'. In this review, the clinical experience gained from the use of autologous hematopoietic stem cell transplantation in treating severe forms of MS are presented, and the current understanding of the mechanisms underlying the mode of action of this treatment, including depletion of disease-mediating immune cells, rejuvenation of the immune repertoire and improvement of regulatory cell function, is discussed.

Expert Rev Hematol. 2009 Dec;2(6):699-715. doi: 10.1586/ehm.09.60.

Autologous hematopoietic stem cell transplantation in autoimmune diseases.

Annaloro C, Onida F, Lambertenghi Deliliers G.

Source

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Abstract

The term 'autoimmune diseases' encompasses a spectrum of diseases whose clinical manifestations and, possibly, biological features vary widely. The results of conventional treatment are considered unsatisfactory in aggressive forms, with subsets of patients having short life expectancies. Relying on wide experimental evidence and more feeble clinical data, some research groups have used autologous hematopoietic stem cell transplantation (HSCT) in the most disabling autoimmune diseases with the aim of resetting the patient's immune system. Immunoablative conditioning regimens are preferred over their myeloablative counterparts, and some form of in vivo and/or ex vivo T-cell depletion is generally adopted. Despite 15 years' experience, published controlled clinical trials are still lacking, with the evidence so far available coming from pilot studies and registry surveys. In multiple sclerosis, clinical improvement, or at least lasting disease stabilization, can be achieved in the majority of the patients; nevertheless, the worst results are observed in patients with progressive disease, where no benefit can be expected from conventional therapy. Concerning rheumatologic diseases, wide experience has been acquired in systemic sclerosis, with long-term improvements in cutaneous disease being frequently reported, although visceral involvement remains unchanged at best. Autografting has proved to be barely effective in rheumatoid arthritis and quite toxic in juvenile idiopathic arthritis, whereas it leads to clinical remission and the reversal of visceral impairment in the majority of patients with systemic lupus erythematosus. A promising indication is Crohn's disease, in which long-term endoscopic remission is frequently observed. Growing experience with autologous HCST in autoimmune diseases has progressively reduced concerns about transplant-related mortality and secondary myelodysplasia/leukemia. Therefore, a sustained complete remission seems to be within the reach of autografting in some autoimmune diseases; in others, the indications, risks and benefits of autografting need to be better defined. Consequently, the search for new drugs should also be encouraged.

Mult Scler. 2011 Feb;17(2):204-13. doi: 10.1177/1352458510383609. Epub 2010 Oct 4.

Autologous hematopoietic cell transplantation for multiple sclerosis: a systematic review.

Reston JT, Uhl S, Treadwell JR, Nash RA, Schoelles K.

Source

Evidence-Based Practice Center, Health Technology Assessment Group, ECRI Institute, Plymouth Meeting, PA, USA. jreston@ecri.org

Abstract

BACKGROUND AND OBJECTIVES:

The purpose of this systematic review was to evaluate the safety and efficacy of autologous hematopoietic cell transplantation in patients with progressive multiple sclerosis (MS) refractory to conventional medical treatment.

METHODS:

Eight case series met our a priori inclusion criteria for the primary outcome of progression-free survival. Individual study quality was rated using an 11-item scale for case series. The strength of the overall body of evidence for each outcome was rated using a system developed by the ECRI Institute. Data from different studies were statistically combined using meta-analysis. An additional six studies were included for a summary of mortality and morbidity.

RESULTS:

For secondary progressive MS, immunoablative therapy with autologous bone marrow/peripheral blood stem cell transplantation was associated with higher progression-free survival (up to 3 years following treatment) when using intermediate-intensity conditioning regimens compared with high-intensity conditioning regimens. The evidence was insufficient to determine whether the treatment was effective in patients with other types of MS. Treatment-related mortality was about 2.7%.

CONCLUSIONS:

Patients with secondary progressive MS refractory to conventional medical treatment have longer progression-free survival following autologous stem cell transplantation with intermediate-intensity conditioning regimens than with high-intensity conditioning regimens.

Ann Hematol. 2011 Mar;90(3):343-8. doi: 10.1007/s00277-010-1071-5. Epub 2010 Sep 25.

Clinical outcome of autologous peripheral blood stem cell transplantation in opticospinal and conventional forms of secondary progressive multiple sclerosis in a Chinese population.

Xu J, Ji BX, Su L, Dong HQ, Sun WL, Wan SG, Liu YO, Zhang P, Liu CY.

Source

Department of Hematology, Xuan Wu Hospital, Capital Medical University, No. 45 Changchun Street, Xuan Wu District, Beijing, China. xujuandail@x263.net

Abstract

To evaluate clinical outcomes of autologous peripheral blood stem cell transplantation (APBCST) between opticospinal multiple sclerosis (OSMS) and conventional multiple sclerosis (CMS) during disease progressive stage in a Chinese population. Thirty-six secondary progressive MS patients, among whom 21 were with OSMS and 15 with CMS, underwent APBSCT and were followed up for an average of 48.92 months (range, 10-91 months). Peripheral blood stem cells were obtained by leukapheresis after mobilization with granulocyte colony-stimulating factor. Modified BEAM conditioning regimen (Tiniposide, melphalan, carmustin, and cytosine arabinoside) were administered. Outcomes were evaluated using the expanded disability status scale (EDSS). No maintenance treatment was administered if there was no disease progression. No treatment-related mortality occurred. Among the 36 patients, one OSMS patient dropped during the follow-up. Among the 22 relapse-free patients, 20 were with continuous neurological improvement without any relapse events, and two remained in neurologically stable states. Among the 13 relapse patients, seven had experienced of neurological relapse, but with no progression during the follow-up period; and six experienced neurological deterioration after transplantation and needed further immunosuppressant treatment. The confirmed relapse-free survival rate was 62.9% and progression-free survival rate was 83.3% after 91 months according to Kaplan and Meier survival curves. Eleven of the 20 OSMS patients (55%) and two of the 15 CMS patients (13.3%) stayed in disease active group (P = 0.014). For the 20 OSMS patients, the overall EDSS score decreased significantly after transplantation (P = 0.016), while visual functions had no significant improvement (P = 0.716). Progressive OSMS has a higher relapse rate than CMS following APBSCT.

Arq Neuropsiquiatr. 2010 Aug;68(4):522-7.

Impact of autologous hematopoetic stem cell transplantation on the quality of life of patients with multiple sclerosis.

Guimarães FA, Oliveira-Cardoso EA, Mastropietro AP, Voltarelli JC, Santos MA.

Source

Post-graduation Program in Psychology, Faculty of Philosophy, Sciences and Letters of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil.

Abstract

OBJECTIVE:

To evaluate the impact of autologous hematopoetic stem cell transplantation (autoHSCT) in the health related quality of life (HRQL) in patients with multiple sclerosis.

METHOD:

The sample consisted of 34 patients, over 18 years old, treated at a University Hospital in the state of São Paulo, Brazil. For data collection MOS SF-36 and EDSS scales were applied at three time points: admission of the patient, hospital discharge and 1 year posttransplantation.

RESULTS:

27 patients (79%) showed stabilization or neurological improvement 1 year posttransplantation. At this time point, there was statistically significant improvement in all domains of the HRQoL. When EDSS scores were correlated with the domains of the MOS SF-36 scale, statistically significant correlations were found with physical functioning at the three time points analysed.

CONCLUSION:

In spite of the high risk of complications of the procedure, the HSCT had positive impact in the health related quality of life.

PMID:

20730303

[PubMed - indexed for MEDLINE]

Free full text

Bone Marrow Transplant. 2010 Dec;45(12):1671-81. doi: 10.1038/bmt.2010.168. Epub 2010 Aug 9.

Hematopoietic SCT for the treatment of multiple sclerosis.

Atkins H.

Source

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Abstract

Multiple sclerosis (MS) is the leading autoimmune indication for autologous hematopoietic SCT (aHSCT). Patient selection criteria and transplant interventions have been refined through a series of cohort and registry studies. High- and low-intensity chemotherapy-based conditioning regimens have been used, creating trade-offs between toxicity and effectiveness. TBI has been associated with greater toxicity and poor outcomes. aHSCT stops MS relapses and lessens the disability in malignant MS, which otherwise rapidly incapacitates patients. Better responses occur in progressive MS earlier in the disease when it has a more inflammatory nature. aHSCT prevents further disability in many patients, but some actually recover from their infirmities. Current regimens and supportive care result in very low morbidity and mortality. MS patients experience unique complications in addition to the expected toxicities. Cytokines used alone for stem-cell mobilization may induce MS flares but are safe to be used in combination with steroids or cytotoxic agents. Urinary tract infections, herpes virus reactivation and an engraftment syndrome may occur early after aHSCT. Rarely secondary autoimmune diseases have been reported late after HSCT. Increasing experience in caring for patients with MS has reduced the frequency and severity of toxicity. Conceived as an opportunity to 'reboot' a tolerant immune system, aHSCT is successful in treating patients with MS that is refractory to conventional immunomodulatory drugs.

Expert Rev Clin Immunol. 2010 May;6(3):347-52. doi: 10.1586/eci.10.7.

Hematopoietic stem cell transplantation in multiple sclerosis: a review of the clinical experience and a report of an international meeting.

Karussis D, Vaknin-Dembinsky A.

Source

Department of Neurology, MS Center and Laboratory of Neuroimmunology, Hadassah Hebrew University Hospital, Jerusalem, IL-91120 Israel. karus@cc.huji.ac.il

Abstract

Hematopoietic stem cell transplantation (HSCT), both allogeneic and autologous, has become one of the hottest topics in clinical immunology. One of the main autoimmune diseases in which HSCT has been extensively tried during the last decade is multiple sclerosis (MS). A few original papers and many anecdotal reports have indicated a beneficial effect of this treatment in MS, leading to stabilization or improvement in a large proportion of the treated patients. However, although hundreds of MS patients have been treated with HSCT, different conditioning and treatment protocols have been used in each center, making it difficult to organize and summarize the results from all of these small studies. Moreover, there is currently no completed controlled study with HSCT in MS. In this review, the cumulative experiences from several centers and countries in the world are summarized, based on the data presented at a recent international meeting in Moscow, Russia, entitled 'Stem Cell Transplantation in Multiple Sclerosis: Sharing the Experience'.

Curr Opin Neurol. 2010 Jun;23(3):218-25. doi: 10.1097/WCO.0b013e328338b7ed.

Stem cell transplantation in multiple sclerosis.

Uccelli A, Mancardi G.

Source

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Abstract

PURPOSE OF REVIEW:

The recent advances in our understanding of stem cell biology, the availability of innovative techniques that allow large-scale acquisition of stem cells, and the increasing pressure from the multiple sclerosis (MS) patient community seeking tissue repair strategies have launched stem cell treatments as one of the most exciting and difficult challenges in the MS field. Here, we provide an overview of the current status of stem cell research in MS focusing on secured actuality, reasonable hopes and unrealistic myths.

RECENT FINDINGS:

Results obtained from small clinical studies with transplantation of autologous hematopoietic stem cells have demonstrated that this procedure is feasible and possibly effective in severe forms of MS but tackles exclusively inflammation without affecting tissue regeneration. Results from preclinical studies with other adult stem cells such as mesenchymal stem cells and neural precursor cells have shown that they may be a powerful tool to regulate pathogenic immune response and foster tissue repair through bystander mechanisms with limited cell replacement. However, the clinical translation of these results still requires careful evaluation.

CONCLUSION:

Current experimental evidence suggests that the sound clinical exploitation of stem cells for MS may lead to novel strategies aimed at blocking uncontrolled inflammation, protecting neurons and promoting remyelination but not at restoring the chronically deranged neural network responsible for irreversible disability typical of the late phase of MS.

Mult Scler. 2010 Jun;16(6):685-93. doi: 10.1177/1352458510364538. Epub 2010 Mar 29.

High-dose immunoablation with autologous haematopoietic stem cell transplantation in aggressive multiple sclerosis: a single centre 10-year experience.

Krasulová E, Trneny M, Kozák T, Vacková B, Pohlreich D, Kemlink D, Kobylka P, Kovárová I, Lhotáková P, Havrdová E.

Source

Department of Neurology, Charles University in Prague, 1st Faculty of Medicine and General Teaching Hospital, Prague, Czech Republic.

Abstract

There are multiple sclerosis patients who suffer from an aggressive course of the disease with severe relapses and rapid accumulation of disability despite adequate treatment. In such cases high-dose immunoablation with autologous haematopoietic stem cell transplantation (ASCT) may be considered. Our objective was to report our experience with 26 multiple sclerosis patients treated with ASCT within the years 1998-2008. Twenty-six patients (Expanded Disability Status Scale 2.5-7.5 (median 6.0), multiple sclerosis duration 2-19 years (median 7)) with aggressive multiple sclerosis underwent autologous haematopoietic stem cell transplantation. Stem cells were mobilized by high-dose cyclophosphamide and granulocyte colony-stimulating factor, BEAM (carmustine, etoposide, cytarabine, melphalan) was used for immunoablation. Patients were evaluated at baseline and every six months post ASCT for adverse events and clinical outcome. Follow-up period was 11-132 months (median 66). Progression-free survival was calculated using the Kaplan- Meier method. At 3 and 6 years of follow-up 70.8% and 29.2% of patients respectively were free of progression. Patients with relapsing multiple sclerosis course, disease duration <5 years and age <35 years had a more favourable outcome. There was no death within 100 days after ASCT. We conclude that ASCT represents a viable and effective treatment option for aggressive multiple sclerosis.

Biol Blood Marrow Transplant. 2010 Aug;16(8):1076-83. doi: 10.1016/j.bbmt.2010.03.012. Epub 2010 Mar 18.

Hematopoietic stem cell transplantation for multiple sclerosis: collaboration of the CIBMTR and EBMT to facilitate international clinical studies.

Pasquini MC, Griffith LM, Arnold DL, Atkins HL, Bowen JD, Chen JT, Freedman MS, Kraft GH, Mancardi GL, Martin R, Muraro PA, Nash RA, Racke MK, Storek J, Saccardi R.

Source

Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin, USA.

Abstract

Clinical investigation of autologous hematopoietic stem cell transplantation (HSCT) as therapy for multiple sclerosis (MS) has been ongoing for over a decade. While several phase II studies have been finalized or are in progress, no definitive prospective randomized studies comparing HSCT versus alternative therapies for MS have been completed. In this conference report of North American and European experts who are involved in the care of MS patients, including neurologists and HSCT physicians, and representatives of the Center for International Blood and Marrow Transplant Research (CIBMTR) and European Group for Blood and Marrow Transplantation (EBMT), we (1) critically review progress to date in HSCT for MS; (2) describe current registry based projects including long-term follow-up studies in HSCT for MS and harmonization of the MS disease-specific research forms that will be used in future by both databases; (3) discuss challenges in study design for a prospective randomized clinical trial of HSCT versus alternative therapy for MS such as feasibility, and the importance of multidisciplinary clinical teams, need for a large sample size and duration of observation required for outcomes assessment; and (4) address future directions in HSCT therapy for MS. To undertake a definitive multicenter clinical trial in autologous HSCT for MS, it will be important to begin well in advance to assemble the team, evaluate proposals for study design, and consider options for the infrastructure and logistical support that will be needed. International collaboration, including partnership with the CIBMTR and EBMT, may be desirable and may in fact be critical for successful completion of a definitive comparative study.

PMID:

20304084

[PubMed - indexed for MEDLINE]

PMCID:

PMC2897916

Mult Scler. 2009 Feb;15(2):229-37. doi: 10.1177/1352458508096875. Epub 2008 Sep 19.

Early highly aggressive MS successfully treated by hematopoietic stem cell transplantation.

Fagius J, Lundgren J, Oberg G.

Source

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Abstract

BACKGROUND:

During the last 15 years, high-dose chemotherapy with autologous hematopoietic stem cell transplantation (HSCT) has globally been performed for severe multiple sclerosis (MS). Most patients have been in progressive phase with long disease duration. As a rule, treatment effect has been minor or moderate.

PATIENTS:

Since 2004, we have performed HSCT in nine young patients with "malignant" relapsing-remitting MS. Criteria for treatment were short duration of disease; very frequent, severe relapses; recent improvement periods indicating potential for recovery after strong immunosuppression.

FINDINGS:

Median age at treatment was 27 (range 9-34) years, MS duration 26 (4-100) months, and annualized relapse rate 10 (4-12). Median Disability Status Scale (extended disability status scale, EDSS) at HSCT was 7.0 (3.5-8.0). Median follow-up time April 2008 is 29 (23-47) months. Median EDSS improvement is 3.5 (1.0-7.0), clearly surpassing most previous reports. One patient relapsed mildly with rapid recovery 7 months after HSCT. All patients are otherwise stable, median EDSS being 2.0 (0-6.0). Before HSCT, 61 relapses occurred in 82 patient months; during follow-up, one relapse in 289 patient months.

CONCLUSION:

This small series of patients with "malignant" relapsing-remitting MS suggests HSCT to be an effective treatment option for this relatively rare disease course. It further suggests that future criteria for HSCT in MS should be close to the present ones.

PMID:

18805841

[PubMed - indexed for MEDLINE]

Expert Rev Hematol. 2009 Dec;2(6):699-715. doi: 10.1586/ehm.09.60.

Autologous hematopoietic stem cell transplantation in autoimmune diseases.

Annaloro C, Onida F, Lambertenghi Deliliers G.

Source

Bone Marrow Transplantation Center-Hematology I, Fondazione Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, University of Milan, Via Francesco Sforza 35, Milan, Italy.

Abstract

The term 'autoimmune diseases' encompasses a spectrum of diseases whose clinical manifestations and, possibly, biological features vary widely. The results of conventional treatment are considered unsatisfactory in aggressive forms, with subsets of patients having short life expectancies. Relying on wide experimental evidence and more feeble clinical data, some research groups have used autologous hematopoietic stem cell transplantation (HSCT) in the most disabling autoimmune diseases with the aim of resetting the patient's immune system. Immunoablative conditioning regimens are preferred over their myeloablative counterparts, and some form of in vivo and/or ex vivo T-cell depletion is generally adopted. Despite 15 years' experience, published controlled clinical trials are still lacking, with the evidence so far available coming from pilot studies and registry surveys. In multiple sclerosis, clinical improvement, or at least lasting disease stabilization, can be achieved in the majority of the patients; nevertheless, the worst results are observed in patients with progressive disease, where no benefit can be expected from conventional therapy. Concerning rheumatologic diseases, wide experience has been acquired in systemic sclerosis, with long-term improvements in cutaneous disease being frequently reported, although visceral involvement remains unchanged at best. Autografting has proved to be barely effective in rheumatoid arthritis and quite toxic in juvenile idiopathic arthritis, whereas it leads to clinical remission and the reversal of visceral impairment in the majority of patients with systemic lupus erythematosus. A promising indication is Crohn's disease, in which long-term endoscopic remission is frequently observed. Growing experience with autologous HCST in autoimmune diseases has progressively reduced concerns about transplant-related mortality and secondary myelodysplasia/leukemia. Therefore, a sustained complete remission seems to be within the reach of autografting in some autoimmune diseases; in others, the indications, risks and benefits of autografting need to be better defined. Consequently, the search for new drugs should also be encouraged.

PMID:

21082959

[PubMed - indexed for MEDLINE]

Neurol Sci. 2009 Oct;30 Suppl 2:S175-7. doi: 10.1007/s10072-009-0144-5.

Autologous haematopoietic stem-cell transplantation in multiple sclerosis: benefits and risks.

Capello E, Vuolo L, Gualandi F, Van Lint MT, Roccatagliata L, Bonzano L, Pardini M, Uccelli A, Mancardi G.

Source

Department of Neuroscience, Ophthalmology and Genetics, University of Genova, Genoa, Italy.

Abstract

Autologous haematopoietic stem-cell transplantation has been evaluated over the last years as a possible new therapeutic strategy in severe forms of multiple sclerosis unresponsive to the approved therapies. Up to now, more than 400 patients have been treated and numerous are the phase I and phase II studies which addressed the feasibility of this treatment, the efficacy, side effects and transplant-related mortality. The clinical response is strongly related to the intensity of the conditioning regimen utilized as well as to the phase of the disease course in which the therapy is carried out. Rapidly evolving multiple sclerosis with a relapsing-remitting clinical course and MRI signs of activity are the cases that can take more advantage. The risk of mortality, which dropped in the last years to 2-3%, is still the main problem of this powerful therapy.

PMID:

19882370

[PubMed - indexed for MEDLINE]

Biol Blood Marrow Transplant. 2010 Jan;16(1 Suppl):S48-56. doi: 10.1016/j.bbmt.2009.10.034. Epub 2009 Nov 4.

Hematopoietic cell transplantation for autoimmune disease: updates from Europe and the United States.

Sullivan KM, Muraro P, Tyndall A.

Source

Division of Cellular Therapy, Duke University Medical Center, Durham, North Carolina 27708, USA.
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Abstract

Considerable advances have been made in our understanding of the immunobiology of autoimmune disease and its treatment with hematopoietic cell transplantation (HCT). In autoimmune disorders, the reconstituted immune system following lymphoablation and autologous HCT yields qualitative changes in immune defects and modifications in adaptive immune responses. Seminal experiments in animals demonstrated that allogeneic or autologous HCT could prevent progression or reverse organ damage from inherited (genetic) or acquired (antigen induced) autoimmune diseases. Convincing animal and clinical data now show that after HCT, the immune system is normalized and "reset". Following autologous transplantation, this resetting occurs via repertoire replacement. It is currently being studied whether and to what extent suppression of inflammation after HCT is due to reregulation of function or due to the eradication of disease associated T and/or B cell populations. There are now a number of published clinical reports with sufficient follow-up for determinations of safety and efficacy of HCT for autoimmune diseases. On behalf of colleagues in the European League Against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT), we review the experience with more than 1000 transplants for autoimmune disease in Europe along with the three major multinational randomized trials in for systemic sclerosis (SSc, the ASTIS study), multiple sclerosis (MS, the ASTIMS study), and Crohn's disease (CD, the ASTIC study). Completed phase II studies in the USA of transplantation for severe SSc, SLE and MS yield promising results. For individuals with SSc, there is dramatic improvement/resolution of dermal fibrosis and stabilization/improvement of pulmonary dysfunction reported up to 8 years after lymphoablative conditioning and autologous HCT. Currently, randomized phase III studies are recruiting subjects in the USA with SSc, MS and CD. In addition, 9 other phase I and II trials in the USA are recruiting patients with autoimmune diseases for nonmyeloablative transplants from allogeneic stem cell donors. Research opportunities abound, but recruitment challenges restrict study entry due to organ impairment from advanced autoimmune disease or insurance denial of coverage for HCT. However, within several NIH sponsored trials there are ongoing immunologic, genomic and mechanistic studies to further understand the molecular mechanisms of autoimmunity, immune regulation and response to treatment. These clinical trials will provide basic scientists with insight into immunoregulatory pathways and clinicians with a context to weigh the progress and evidence in this evolving treatment for autoimmune diseases.

PMID:

19895895

[PubMed - indexed for MEDLINE]

PMCID:

PMC3448948

Bone Marrow Transplant. 2010 Jun;45(6):1014-21. doi: 10.1038/bmt.2009.305. Epub 2009 Oct 26.

Autologous haematopoietic stem cell transplantation for secondary progressive multiple sclerosis: an exploratory cost-effectiveness analysis.

Tappenden P, Saccardi R, Confavreux C, Sharrack B, Muraro PA, Mancardi GL, Kozak T, Farge-Bancel D, Madan J, Rafia R, Akehurst R, Snowden J.

Source

Health Economics and Decision Science (HEDS), School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK. p.tappenden@sheffield.ac.uk

Abstract

Treatment options for secondary progressive multiple sclerosis (SPMS) are limited. Mitoxantrone is routinely used to stabilize disease progression; however, evolving evidence suggests clinical benefit from intensive treatment with autologous haematopoietic stem cell transplantation (HSCT). Given differences in cost and outcomes, preliminary cost-effectiveness studies are warranted if this approach is to be developed for more widespread application in SPMS. We developed a decision-analytic Markov model to explore the potential cost-effectiveness of autologous HSCT versus mitoxantrone in SPMS, using patient-level data from registry sources. The model evaluates the lifetime costs and health outcomes associated with disability progression and relapse. Sensitivity analyses were undertaken to examine the uncertainty surrounding cost-effectiveness outcomes. In the absence of randomised controlled trial (RCT) evidence, conditions for comparative analysis were not ideal. Under optimistic assumptions, HSCT is estimated to cost below pound3000 per quality adjusted life year gained. However, when a strict 6-month sustained progression rule is adopted, HSCT may be less effective and more expensive than mitoxantrone. The model results were sensitive to reducing procedural costs and HSCT-related mortality. We conclude that HSCT could potentially achieve an acceptable level of cost-effectiveness. However, caution should be exercised as large, high-quality RCTs comparing HSCT versus mitoxantrone are necessary to validate these findings.

PMID:

19855441

[PubMed - indexed for MEDLINE]

Acta Neurol Scand. 2009 Dec;120(6):371-82. doi: 10.1111/j.1600-0404.2009.01168.x. Epub 2009 Sep 24.

Hematopoietic stem cell transplantation in multiple sclerosis.

Rogojan C, Frederiksen JL.

Source

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Abstract

Intensive immunosuppresion followed by hematopoietic stem cell transplantation (HSCT) has been suggested as potential treatment in severe forms of multiple sclerosis (MS). Since 1995 ca. 400 patients have been treated with HSCT. Stabilization or improvement occurred in almost 70% of cases at least for 3 years post-transplant. Magnetic resonance revealed the capacity of autologous HSCT to suppress or markedly reduce gadolinium-enhancing lesions. The progression of brain atrophy declined after two years post-HSCT. The profound immunological changes following autologous HSCT may result in restoration of self-tolerance. Relatively young patients with active inflammatory lesions of relatively short duration and rapidly progressive disease, but still low disability scores, unresponsive to conventional therapy seem the best candidates for transplantation. Transplant-related mortality was 6% in the first EBMT report and 5.3% in the second one. No deaths were reported since 2001. Very high-intensity conditioning regimen is associated with higher risk of toxicity without significant increase in efficacy. The effects of transplantation and transplantation-related morbidity are dependent on patient-selection, time of transplantation and conditioning regimens used.This review is a comprehensive study of the results obtained in several single-center and multicenter studies. Patient characteristics, transplantations steps, toxicity and clinical outcome have been monitored and compared.

PMID:

19785643

[PubMed - indexed for MEDLINE]

Haematologica. 2010 Feb;95(2):284-92. doi: 10.3324/haematol.2009.013458. Epub 2009 Sep 22.

Autologous hematopoietic stem cell transplantation for autoimmune diseases: an observational study on 12 years' experience from the European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases.

Farge D, Labopin M, Tyndall A, Fassas A, Mancardi GL, Van Laar J, Ouyang J, Kozak T, Moore J, Kötter I, Chesnel V, Marmont A, Gratwohl A, Saccardi R.

Source

Service de Médecine Interne et Unité INSERM U 976, Hôpital Saint-Louis, Assistance-Publique Hôpitaux de Paris, Paris-7 Université Denis Diderot, 1 avenue Claude Vellefaux, 75 010 Paris France. dominique.farge-bancel@sls.ap-hop-paris.fr.

Abstract

BACKGROUND:

Autologous hematopoietic stem cell transplantation has been used since 1996 for the treatment of severe autoimmune diseases refractory to approved therapies. We evaluated the long-term outcomes of these transplants and aimed to identify potential prognostic factors.

DESIGN AND METHODS:

In this observational study we analyzed all first autologous hematopoietic stem cell transplants for autoimmune diseases reported to the European Group for Blood and Marrow Transplantation registry between 1996-2007. The primary end-points for analysis were overall survival, progression-free survival and transplant-related mortality at 100 days.

RESULTS:

Nine hundred patients with autoimmune diseases (64% female; median age, 35 years) who underwent a first autologous hematopoietic stem cell transplant were included. The main diseases were multiple sclerosis (n=345), systemic sclerosis (n=175), systemic lupus erythematosus (n=85), rheumatoid arthritis (n=89), juvenile arthritis (n=65), and hematologic immune cytopenia (n=37). Among all patients, the 5-year survival was 85% and the progression-free survival 43%, although the rates varied widely according to the type of autoimmune disease. By multivariate analysis, the 100-day transplant-related mortality was associated with the transplant centers' experience (P=0.003) and type of autoimmune disease (P=0.03). No significant influence of transplant technique was identified. Age less than 35 years (P=0.004), transplantation after 2000 (P=0.0015) and diagnosis (P=0.0007) were associated with progression-free survival.

CONCLUSIONS:

This largest cohort studied worldwide shows that autologous hematopoietic stem cell transplantation can induce sustained remissions for more than 5 years in patients with severe autoimmune diseases refractory to conventional therapy. The type of autoimmune disease, rather than transplant technique, was the most relevant determinant of outcome. Results improved with time and were associated with the transplant centers' experience. These data support ongoing and planned phase III trials to evaluate the place of autologous hematopoietic stem cell transplantation in the treatment strategy for severe autoimmune diseases.

PMID:

19773265

[PubMed - indexed for MEDLINE]

Bone Marrow Transplant. 2010 Feb;45(2):239-48. doi: 10.1038/bmt.2009.127. Epub 2009 Jul 6.

Brazilian experience with two conditioning regimens in patients with multiple sclerosis: BEAM/horse ATG and CY/rabbit ATG.

Hamerschlak N, Rodrigues M, Moraes DA, Oliveira MC, Stracieri AB, Pieroni F, Barros GM, Madeira MI, Simões BP, Barreira AA, Brum DG, Ribeiro AA, Kutner JM, Tylberi CP, Porto PP, Santana CL, Neto JZ, Barros JC, Paes AT, Burt RK, Oliveira EA, Mastropietro AP, Santos AC, Voltarelli JC.

Source

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Abstract

Studies have shown that autologous hematopoietic SCT (HSCT) can be used as an intensive immunosuppressive therapy to treat refractory patients and to prevent the progression of multiple sclerosis (MS). This is a prospective multicentric Brazilian MS trial comparing two conditioning regimens: BEAM/horse ATG and CY/rabbit ATG. Most (80.4%) of the 41 subjects in the study had the secondary progressive MS subtype and the mean age was 42 years. The baseline EDSS score in 58.5% of the subjects was 6.5 and 78% had a score of 6.0 or higher, respectively. The complication rate during the intra-transplantation period was 56% for all patients: 71.4% of the patients in the BEAM/hATG group and 40% in the CY/rATG group (P=0.04). Three subjects (7.5%) died of cardiac toxicity, sepsis and alveolar hemorrhage, all of them in the BEAM/ATG group. EFS was 58.54% for all patients: 47% in the BEAM/hATG group and 70% in the CY/rATG group (P=0.288). In conclusion, the CY/rATG regimen seems to be associated with similar outcome results, but presented less toxicity when compared with the BEAM/hATG regimen. Long-term follow-up would be required to fully assess the differences in therapeutic effectiveness between the two regimens.

PMID:

19584827

[PubMed - indexed for MEDLINE]

Z Rheumatol. 2009 May;68(3):214-5, 217-9. doi: 10.1007/s00393-008-0392-4.

[Stem cell therapy in multiple sclerosis: a clinical update].

[Article in German]

Schippling S, Martin R.

Source

Zentrum für Molekulare Neurobiologie, Institut für Neuroimmunologie und Klinische Multiple Sklerose Forschung (INIMS), Falkenried 3, 20246, Hamburg, Deutschland. s.schippling@uke.uni-hamburg.de

Abstract

Promising results in an animal model of multiple sclerosis (MS; experimental autoimmune encephalomyelitis, EAE) have shown that immunosuppression followed by allogeneic bone marrow transplantation has the potential to significantly ameliorate the spontaneous course of the disease. Since 1995, emerging data on autologous hematopoietic stem cell transplantation (AHSCT) has supported a benefit also in patients with multiple sclerosis. To date, results on approximately 500 cases have been consecutively reported by the European Group for Blood and Marrow Transplantation (EBMT). These reports have not only proved a favourable outcome for many patients but also provided the rationale for the currently ongoing controlled trials on AHSCT in MS. At present, results from the ASTIMS study in particular, a multicenter active-controlled phase II study, are awaited. However, a number of critical issues remain unresolved. Furthermore, with upcoming new treatment compounds that to some extent act via lymphoablative properties, it remains essential to better select those patients who might profit most from stem cell therapy based on a justifiable benefit-to-risk ratio. Although transplant related mortality has dropped to 1%, mortality combined with concerns about long-term safety remain critical issues in a primarily non-life-threatening disease like MS.

PMID:

19399509

[PubMed - indexed for MEDLINE]

Methods Mol Biol. 2009;549:231-46. doi: 10.1007/978-1-60327-931-4_16.

Immune ablation followed by autologous hematopoietic stem cell transplantation for the treatment of poor prognosis multiple sclerosis.

Atkins H, Freedman M.

Source

The Ottawa Hospital Blood and Marrow Transplant Program, Ottawa, Ontario, ON, Canada.

Abstract

Complete abrogation of the inflammatory response by high-dose cytotoxic therapy at an early stage of MS, when the nervous system has not yet sustained irreparable damage may be successful at preventing the inexorable progression. Immunological and hematological reconstitution follows abrogation through bone marrow transplantation. The issues are complex, and many factors, including baseline disability, the timing of this intervention, the intensity of the immune ablation, and depletion of lymphocytes from the graft, are all likely to influence treatment outcome. This article describes the immune ablation regimen for treatment of patients with poor prognosis MS, as performed in the Canadian MS-BMT study.

PMID:

19378207

[PubMed - indexed for MEDLINE]

Lancet Neurol. 2009 Mar;8(3):244-53. doi: 10.1016/S1474-4422(09)70017-1. Epub 2009 Jan 29.

Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting MS: a phase I/II study.

Burt RK, Loh Y, Cohen B, Stefoski D, Balabanov R, Katsamakis G, Oyama Y, Russell EJ, Stern J, Muraro P, Rose J, Testori A, Bucha J, Jovanovic B, Milanetti F, Storek J, Voltarelli JC, Burns WH.

Source

Division of Immunotherapy, Department of Medicine, Northwestern University, Chicago, IL 60611, USA. rburt@northwestern.edu

Abstract

BACKGROUND:

Autologous non-myeloablative haemopoietic stem cell transplantation is a method to deliver intense immune suppression. We evaluated the safety and clinical outcome of autologous non-myeloablative haemopoietic stem cell transplantation in patients with relapsing-remitting multiple sclerosis (MS) who had not responded to treatment with interferon beta.

METHODS:

Eligible patients had relapsing-remitting MS, attended Northwestern Memorial Hospital, and despite treatment with interferon beta had had two corticosteroid-treated relapses within the previous 12 months, or one relapse and gadolinium-enhancing lesions seen on MRI and separate from the relapse. Peripheral blood haemopoietic stem cells were mobilised with 2 g per m2 cyclophosphamide and 10 microg per kg per day filgrastim. The conditioning regimen for the haemopoietic stem cells was 200 mg per kg cyclophosphamide and either 20 mg alemtuzumab or 6 mg per kg rabbit antithymocyte globulin. Primary outcomes were progression-free survival and reversal of neurological disability at 3 years post-transplantation. We also sought to investigate the safety and tolerability of autologous non-myeloablative haemopoietic stem cell transplantation.

FINDINGS:

Between January, 2003, and February, 2005, 21 patients were treated. Engraftment of white blood cells and platelets was on median day 9 (range day 8-11) and patients were discharged from hospital on mean day 11 (range day 8-13). One patient had diarrhoea due to Clostridium difficile and two patients had dermatomal zoster. Two of the 17 patients receiving alemtuzumab developed late immune thrombocytopenic purpura that remitted with standard therapy. 17 of 21 patients (81%) improved by at least 1 point on the Kurtzke expanded disability status scale (EDSS), and five patients (24%) relapsed but achieved remission after further immunosuppression. After a mean of 37 months (range 24-48 months), all patients were free from progression (no deterioration in EDSS score), and 16 were free of relapses. Significant improvements were noted in neurological disability, as determined by EDSS score ($p<0.0001$), neurological rating scale score ($p=0.0001$), paced auditory serial addition test ($p=0.014$), 25-foot walk ($p<0.0001$), and quality of life, as measured with the short form-36 (SF-36) questionnaire ($p<0.0001$).

INTERPRETATION:

Non-myeloablative autologous haemopoietic stem cell transplantation in patients with relapsing-remitting MS reverses neurological deficits, but these results need to be confirmed in a randomised trial.

PMID: 19186105

Autoimmunity. 2008 Dec;41(8):601-10. doi: 10.1080/08916930802197347.

Autologous hemopoietic stem cell transplantation for multiple sclerosis: is it worthwile?

Fassas A, Mancardi GL.

Source

Cell and Gene Therapy Unit, Department of Hematology and Bone Marrow Transplantation, The George Papanicolaou Hospital, Thessaloniki, Greece. hempap@otenet.gr

Abstract

High-dose immunosuppressive chemotherapy or total body irradiation followed by autologous transplantation of hemopoietic stem cells (ASCT) was introduced in the treatment of active, progressing, and therapy-resistant multiple sclerosis (MS) in 1995. Since then, more than 300 patients have undergone this sort of treatment worldwide and the European Group for Blood and Marrow Transplantation (EBMT) published on two occasions, in 2002 and in 2006, the results of collective analyses performed in 85 and in 183 cases, respectively. In most communications the results were reported favorable with some cases showing spectacular recoveries and also probabilities of long-lasting disease stability, between 60 and 80% at three years after transplant. Of great interest was the fact that magnetic resonance imaging studies invariably showed that the inflammation in the central nervous system resolved and gadolinium-enhancing lesions were completely abolished or markedly reduced. These results appear superior to those yielded by standard therapies but this superiority needs to be demonstrated by comparative studies, such as the EBMT-launched ASTIMS trial. Moreover, ASCT is a rather toxic procedure associated with a mortality risk of 2-3%. Therefore, it is not a treatment for the general population of MS patients but only for selected cases that do not respond to standard therapies and worsen rapidly, i.e. in situations where benefits are expected to counterbalance morbidity and mortality risks. Nevertheless, certain issues seem to have cleared up: ASCT should be used early, during the inflammatory phase of the disease; very high-intensity pre-transplant conditioning regimens increase toxicity but do not seem to increase efficacy compared to intermediate-intensity regimens; the results are dramatic and life-saving in resistant, so-called "malignant" cases; ASCT does not only cause debulking of autoreactive clones but it also brings about qualitative immunological changes that might eventually establish immunologic self-tolerance; the progression of brain atrophy appears to slow down with time; with the implementation of proper patient-selection criteria, the risks of morbidity and mortality can be minimized.

PMID:

18958762

[PubMed - indexed for MEDLINE]

Curr Opin Hematol. 2008 Nov;15(6):594-600. doi: 10.1097/MOH.0b013e3283136700.

Haematopoietic stem cell transplantation for autoimmune disorders.

Saccardi R, Di Gioia M, Bosi A.

Source

Department of Haematology, Careggi Hospital, University of Florence, Florence, Italy. r.saccardi@dac.unifi.it

Abstract

PURPOSE OF REVIEW:

To summarize recent evidence and current trends in the use of haematopoietic stem cell transplantation (HSCT) for autoimmune diseases.

RECENT FINDINGS:

Updates of published trials and data from the registries indicate a long-lasting, immunosuppression-free condition in about 50% of the patients who underwent an HSCT for a severe, progressive autoimmune disease. For all diseases, autologous HSCT is largely preferred for safety reasons, whereas allogeneic HSCT is to be considered only for carefully selected cases. Transplant-related mortality (TRM) has decreased in the past 5 years, due to both better selection of patients and the use of less intensive conditioning regimens. The most employed conditioning regimens in Europe are BCNU (carmustine), etoposide, ARA-C (cytosine arabinoside), M (melphalan) (BEAM)/anti-thymocyte globulin in multiple sclerosis and high-dose cyclophosphamide/anti-thymocyte globulin for all other diseases, with a trend for more intense regimens in North America. Multiple sclerosis and systemic sclerosis are currently the most frequent diagnoses. Prospective comparative trials are currently ongoing both in Europe and North America.

SUMMARY:

Recent reports confirm the evidence that HSCT is able to induce a high rate of sustained remissions in most severe autoimmune diseases, unresponsive to conventional treatments. Valuable information is expected by the finalization of the ongoing prospective, comparative trials.

PMID:

18832930

[PubMed - indexed for MEDLINE]

Neurologia. 2008 Sep;23(7):405-7.

[Clinical outcome 6 years after autologous hematopoietic stem cell transplantation in multiple sclerosis].

[Article in Spanish]

Saiz A, Blanco Y, Berenguer J, Gómez-Choco M, Carreras E, Arbizu T, Graus F.

Source

Servicio de Neurología, Hematología Hospital Clínic, Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona. asaiz@clinic.ub.es

Abstract

INTRODUCTION:

Autologous hematopoietic stem cell transplantation (AHSCT) remains as an experimental treatment for severe forms of multiple sclerosis (MS). We describe the clinical outcome of 14 patients included in a protocol of AHSCT after a median follow-up period of 6 years.

METHODS:

14 patients (5 relapsing-remitting and 9 secondary progressive) with a median number of relapses in the year before of 3 (1-7), Expanded Disability Status Scale (EDSS) of 6 (4.5-6.5) and decile of the multiple Sclerosis Severity Store (MSSS) 9 (7-10) were included. The procedure included carmustine, cyclophosphamide, antithymocyte globulin and T-cell depletion by CD34+ selection.

RESULTS:

The 4.5-year progression-free survival was 71%. The 6 year actuarial probability of progression-free survival was 62.5% and the disease activity-free survival of 7.1%. The median EDSS was 6 (4-8.5) and the MSSS 8 (5-10). Only 2 patients presented enhanced T1 lesions. No long-term complications related to the procedure were observed.

CONCLUSION:

AHSCT cannot be deemed a curative treatment but may cause prolonged stabilisation or change the aggressive course of the disease.

PMID:

18726717

[PubMed - indexed for MEDLINE]

Lancet Neurol. 2008 Jul;7(7):626-36. doi: 10.1016/S1474-4422(08)70138-8.

Autologous haematopoietic stem-cell transplantation in multiple sclerosis.

Mancardi G, Saccardi R.

Source

Department of Neuroscience, Ophthalmology, and Genetics, and Centre of Excellence for Biomedical Research, San Martino Hospital, University of Genoa, Genoa, Italy. glmancardi@neurologia.unige.it

Abstract

Intense immunosuppression followed by autologous haematopoietic stem-cell transplantation has been assessed over the past few years as a possible new therapeutic strategy in severe forms of multiple sclerosis. Pioneering studies began in 1995, and since then, more than 400 patients worldwide have been treated with this procedure. Small uncontrolled studies show that about 60-70% of treated cases do not progress in the follow-up period of at least 3 years. Transplant-related mortality, which was 5-6% in the first reported series, has reduced in the past 5 years to 1-2%. Relapses dramatically decrease and inflammatory MRI activity is almost completely suppressed. Autologous haematopoietic stem-cell transplantation is associated with qualitative immunological changes in the blood, suggesting that, beyond its immunosuppressive potential, it could also have some beneficial effect for the resetting of the immune system. Patients with severe, rapidly worsening multiple sclerosis who are unresponsive to approved therapies could be candidates for this treatment, but its clinical efficacy has still to be shown in large, prospective, controlled studies.

PMID:

18565456

[PubMed - indexed for MEDLINE]

Exp Hematol. 2008 Aug;36(8):922-8. doi: 10.1016/j.exphem.2008.03.001. Epub 2008 May 12.

High-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation as a treatment option in multiple sclerosis.

Shevchenko YL, Novik AA, Kuznetsov AN, Afanasiev BV, Lisukov IA, Kozlov VA, Rykavicin OA, Ionova TI, Melnichenko VY, Fedorenko DA, Kulagin AD, Shamanski SV, Ivanov RA, Gorodokin G.

Source

Pirogov National Medical Surgical Center, the Department of Haematology and Cellular Therapy, Pirogov National Medical Surgical Center, Moscow, Russia.

Abstract

High-dose immunosuppressive therapy (HDIT) with autologous hematopoietic stem cell transplantation (auto-HSCT) is a new and promising approach to the treatment of multiple sclerosis (MS) patients because currently there are no effective treatment methods for this disease. In this article, we present results of a prospective clinical study of efficacy of HDIT + auto-HSCT in MS patients. The following treatment strategies were employed in the study: "early," "conventional," and "salvage/late" transplantation. Fifty patients with various types of MS were included in this study. No toxic deaths were reported among 50 MS patients; transplantation procedure was well-tolerated by the patients. The efficacy analysis was performed in 45 patients. Twenty-eight patients achieved an objective improvement of neurological symptoms, defined as at least 0.5-point decrease in the Expanded Disability Status Scale (EDSS) score as compared to the baseline and confirmed during 6 months, and 17 patients had disease stabilization (steady EDSS level as compared to the baseline and confirmed during 6 months). The progression-free survival at 6 years after HDIT + auto-HSCT was 72%. Magnetic resonance imaging data were available in 37 patients before transplantation showing disease activity in 43.3%. No active, new, or enlarging lesions were registered in patients without disease progression. In conclusion, HDIT + auto-HSCT suggests positive results in management of patients with different types of MS. Identification of treatment strategies based on the level of disability, namely "early," "conventional," and "salvage/late" transplantation, appears to be feasible to improve treatment outcomes.

PMID:

18468768

[PubMed - indexed for MEDLINE]

Lancet Neurol. 2008 Feb;7(2):173-83. doi: 10.1016/S1474-4422(08)70020-6.

Intense immunosuppression in patients with rapidly worsening multiple sclerosis: treatment guidelines for the clinician.

Boster A, Edan G, Frohman E, Javed A, Stuve O, Tselis A, Weiner H, Weinstock-Guttman B, Khan O; Multiple Sclerosis Clinical Research Center, Department of Neurology, Wayne State University School of Medicine.

Source

The Multiple Sclerosis Clinical Research Center, Department of Neurology, Wayne State University School of Medicine, and The Detroit Medical Center, Detroit, MI 48201, USA.

Abstract

Several lines of evidence link immunosuppression to inflammation in patients with multiple sclerosis (MS) and provide a rationale for the increasing use of immunosuppressive drugs in the treatment of MS. Treatment-refractory, clinically active MS can quickly lead to devastating and irreversible neurological disability and treating these patients can be a formidable challenge to the clinician. Patients with refractory MS have been treated with intense immunosuppression, such as cyclophosphamide or mitoxantrone, or with autologous haematopoeitic stem cell transplants. Evidence shows that intense immunosuppression might be effective in patients who are unresponsive to immunomodulating therapy, such as interferon beta and glatiramer acetate. Natalizumab, a new addition to the armamentarium for treating MS, might also have a role in the treatment of this MS phenotype. This Review describes the use of intense immunosuppressant drugs and natalizumab in patients with rapidly worsening MS and provides clinicians with guidelines for the use of these drugs in this patient group.

PMID:

18207115

[PubMed - indexed for MEDLINE]

Semin Hematol. 2007 Oct;44(4):278-85.

Autologous stem cell transplantation in autoimmune diseases.

Passweg J, Tyndall A.

Source

Division of Hematology, University Hospital Geneva, Geneva, Switzerland.

Abstract

Since 1996, approximately 1,000 patients have received an autologous hematopoietic stem cell transplant (HSCT) as treatment for a severe autoimmune disease (AD). The European Group for Blood and Marrow Transplantation (EBMT)/European League Against Rheumatism (EULAR) Autoimmune Disease Working Party have registered more than 800 patients and works in close collaboration with networks in the United States where several hundred more AD patients have been similarly transplanted. The majority of ADs were multiple sclerosis (MS), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile idiopathic arthritis, and immune cytopenias. Many patients have experienced long-term disease-free remissions and immune reconstitution studies have shown in some cases that a "resetting" of autoimmunity is possible. The initially high treatment-related mortality (TRM) is reduced significantly in the later years, and the phase I/II experience is now being verified in several international prospective randomized clinical trials. In addition, the past several years have seen a growing interest in the role and potential therapeutic application of mesenchymal stem cells (MSC) in the immunomodulation of AD, as in the early experience with acute-graft-versus host disease (GvHD).

PMID:

17961728

[PubMed - indexed for MEDLINE]

Mult Scler. 2008 Mar;14(2):278-83. Epub 2007 Oct 17.

Autologous stem-cell transplantation in malignant multiple sclerosis: a case with a favorable long-term outcome.

Kimiskidis V, Sakellari I, Tsimourtou V, Kapina V, Papagiannopoulos S, Kazis D, Vlaikidis N, Anagnostopoulos A, Fassas A.

Source

Department of Neurology III, Aristotle University of Thessaloniki, George Papanikolaou Hospital, Thessaloniki, 570 10 Greece. kimiskid@med.auth.gr

Abstract

Malignant multiple sclerosis (MS) is a rare but clinically important subtype of MS characterized by the rapid development of significant disability in the early stages of the disease process. These patients are refractory to conventional immunomodulatory agents and the mainstay of their treatment is plasmapheresis or immunosuppression with mitoxantrone, cyclophosphamide, cladribine or, lately, bone marrow transplantation. We report on the case of a 17-year old patient with malignant MS who was treated with high-dose chemotherapy plus anti-thymocyte globulin followed by autologous stem cell transplantation. This intervention resulted in an impressive and long-lasting clinical and radiological response. It is concluded that intensive immunosuppression followed by autologous stem cell transplantation is a viable therapeutic option in patients with malignant MS unresponsive to conventional forms of treatment.

PMID:

17942513

[PubMed - indexed for MEDLINE]

Neurotherapeutics. 2007 Oct;4(4):676-92.

Emerging therapies for multiple sclerosis.

Muraro PA, Bielekova B.

Source

Department of Cellular and Molecular Neuroscience, Imperial College London, London SW7 2AZ, United Kingdom. p.murano@imperial.ac.uk

Abstract

This review examines the mode of action, safety profile and clinical efficacy of some of the most promising new therapeutic strategies for multiple sclerosis. Autologous hematopoietic stem cell transplantation can regenerate a new and tolerant immune system and is a potentially effective rescue therapy in a subset of patients with aggressive forms of MS refractory to approved immunomodulatory and immunosuppressive agents. High-dose cyclophosphamide without stem cell support is suggested to induce prolonged remissions through similar immunological mechanisms with less toxicity. Fingolimod (FTY720) is a novel oral immunomodulating agent that acts through preventing lymphocyte recirculation from lymphoid organs. Monoclonal antibody therapy has provided scientists and clinicians the opportunity to rationally direct the therapeutic intervention against specific molecules. Targeting molecules of the immune system such as CD52 (alemtuzumab), CD25 (daclizumab), VLA-4 (natalizumab) and CD20 (rituximab) have resulted in potent immunomodulatory effects through sometimes unpredicted mechanisms. The potential of immunoglobulins to induce remyelination in the CNS is being investigated in an attempt to develop therapies promoting tissue repair and functional recovery. The evidence supporting the potential of these emerging immunotherapies suggests that strong progress is being made in the development of effective cures for multiple sclerosis.

PMID:

17920549

[PubMed - indexed for MEDLINE]

Ann Acad Med Singapore. 2007 Jun;36(6):421-6.

Autologous haematopoietic stem cell transplantation for the treatment of multiple sclerosis.

Loh YS, Hwang WY, Ratnagopal P.

Source

Department of Haematology, Singapore General Hospital, Singapore. yvonne.loh.s.m@sgh.com.sg

Abstract

INTRODUCTION:

Autologous haematopoietic stem cell transplantation (auto-HSCT) has been performed for severe multiple sclerosis (MS) refractory to standard therapy with increasing frequency worldwide. However, experience in Asia employing this modality in MS has been limited. In this review, we explored the pathophysiology of autoimmunity and the underlying rationale for auto-HSCT in treating autoimmune diseases including MS, as well as existing published pre-clinical and clinical data. We aimed thereby to better understand the utility of treating MS with auto-HSCT and the feasibility of this procedure in Singapore.

METHODS:

A Medline search was performed with the terms "haematopoietic stem cell transplantation", "multiple sclerosis" and "autoimmune diseases" from 1996 to 2005. Both original papers and review articles were considered.

MAIN FINDINGS:

The majority of publications were from Europe or the United States and most clinical series from single centres had relatively small numbers of patients. Worldwide, the number of patients reported has been less than 300 since 1997. Existing data support the feasibility and promise of this procedure and ongoing Phase III trials may serve to confirm this initial experience.

CONCLUSION:

Pre-clinical and early clinical data support the rationale for immunoablative therapy for autoimmune disorders. Auto-HSCT for severe MS is a feasible procedure and can be safely performed in centres with experience managing HSCT patients.

PMID:

17597968

[PubMed - indexed for MEDLINE]

Mult Scler. 2007 Jun;13(5):676-8. Epub 2007 Feb 16.

Autologous hematopoietic stem cell transplantation for very active relapsing-remitting multiple sclerosis: report of two cases.

Portaccio E, Amato MP, Siracusa G, Pagliai F, Sorbi S, Guidi S, Bosi A, Saccardi R.

Source

Department of Neurology, University of Florence, and Bone Marrow Transplantation Unit, Careggi Hospital, Florence, Italy. portilio@tin.it

Abstract

Autologous hematopoietic stem cell transplantation (AHSCT) has been proposed as a rescue treatment in multiple sclerosis (MS) patients not responding to first- or second-line therapies. To date, most of the treated cases had a secondary progressive disease course. However, patients with high inflammatory activity, but no secondary progression of the disease, could be candidates to take greater advantage of AHSCT. In this paper, we report two cases with very active, relapsing-remitting (RR) MS, who underwent AHSCT, and obtained a dramatic resolution to disease activity.

PMID:

17548451

[PubMed - indexed for MEDLINE]

Mult Scler. 2007 Sep;13(8):1068-70. Epub 2007 Apr 27.

The long-term effect of AHSCT on MRI measures of MS evolution: a five-year follow-up study.

Roccatagliata L, Rocca M, Valsasina P, Bonzano L, Sormani M, Saccardi R, Mancardi G, Filippi M; Italian GITMO-NEURO Intergroup on Autologous Stem Cell Transplantation.

Source

Department of Neuroscience, Ophtalmology and Genetics, University of Genoa, Genoa.

Abstract

Using MRI, we measured disease activity and brain atrophy in nine multiple sclerosis patients treated with autologous hematopoietic stem cell transplantation (AHSCT) for a mean follow up of 63 months. We show that AHSCT is associated to a longlasting suppression of inflammation and to a marked decrease of the rate of brain atrophy after the second year following treatment.

PMID:

17468445

[PubMed - indexed for MEDLINE]

Mult Scler. 2006 Dec;12(6):814-23.

Autologous stem cell transplantation for progressive multiple sclerosis: update of the European Group for Blood and Marrow Transplantation autoimmune diseases working party database.

Saccardi R, Kozak T, Bocelli-Tyndall C, Fassas A, Kazis A, Havrdova E, Carreras E, Saiz A, Löwenberg B, te Boekhorst PA, Gualandio F, Openshaw H, Longo G, Pagliai F, Massacesi L, Deconink E, Ouyang J, Nagore FJ, Besalduch J, Lisukov IA, Bonini A, Merelli E, Slavino S, Gratwohl A, Passweg J, Tyndall A, Steck AJ, Andolina M, Capobianco M, Martin JL, Lugaresi A, Meucci G, Sáez RA, Clark RE, Fernandez MN, Fouillard L, Herstenstein B, Koza V, Cocco E, Baurmann H, Mancardi GL; Autoimmune Diseases Working Party of EBMT.

Source

BMT Unit Department of Hematology, Ospedale di Careggi, Florence, Italy. r.saccardi@DAC.UNIFI.IT

Abstract

Over the last decade, hematopoietic stem cells transplantation (HSCT) has been increasingly used in the treatment of severe progressive autoimmune diseases. We report a retrospective survey of 183 multiple sclerosis (MS) patients, recorded in the database of the European Blood and Marrow Transplantation Group (EBMT). Transplant data were available from 178 patients who received an autologous graft. Overall, transplant related mortality (TRM) was 5.3% and was restricted to the period 1995-2000, with no further TRM reported since then. Busulphan-based regimens were significantly associated with TRM. Clinical status at the time of transplant and transplant techniques showed some correlations with toxicity. No toxic deaths were reported among the 53 patients treated with the BEAM (carmustine, etoposide, cytosine-arabinoside, melphalan)/antithymocyte globulin (ATG) regimen without graft manipulation, irrespective of their clinical condition at the time of the transplant. Improvement or stabilization of neurological conditions occurred in 63% of patients at a median follow-up of 41.7 months, and was not associated with the intensity of the conditioning regimen. In this large series, HSCT was shown as a promising procedure to slow down progression in a subset of patients affected by severe, progressive MS; the safety and feasibility of the procedure can be significantly improved by appropriate patient selection and choice of transplant regimen.

PMID:

17263012

[PubMed - indexed for MEDLINE]

Chin Med J (Engl). 2006 Nov 20;119(22):1851-5.

Clinical outcomes after autologous haematopoietic stem cell transplantation in patients with progressive multiple sclerosis.

Xu J, Ji BX, Su L, Dong HQ, Sun XJ, Liu CY.

Source

Department of Haematology, Xuanwu Hospital, Capital University of Medical Sciences, Beijing 100053, China. xujuandail@x263.net

Abstract

BACKGROUND:

Multiple sclerosis (MS) is a continuously disabling disease and it is unresponsive to high dose steroid and immunomodulation with disease progression. The autologous haematopoietic stem cell transplantation (ASCT) has been introduced in the treatment of refractory forms of multiple sclerosis. In this study, the clinical outcomes followed by ASCT were evaluated for patients with progressive MS.

METHODS:

Twenty-two patients with secondary progressive MS were treated with ASCT. Peripheral blood stem cells were obtained by leukapheresis after mobilization with granulocyte colony stimulating factor. Etoposide, melphalan, carmustin and cytosine arabinoside were administered as conditioning regimen. Outcomes were evaluated by the expanded disability status scale and progression free survival. No maintenance treatment was administered during a median follow-up of 39 months (range, 6 to 59 months).

RESULTS:

No death occurred following the treatment. The overall confirmed progression free survival rate was 77% up to 59 months after transplantation which was significantly higher compared with pre-transplantation (P = 0.000). Thirteen patients (59%) had remarkable improvement in neurological manifestations, four (18%) stabilized their disability status and five (23%) showed clinical recurrence of active symptoms.

CONCLUSIONS:

ASCT as a therapy is safe and available. It can improve or stabilize neurological manifestations in most patients with progressive MS following failure of conventional therapy.

PMID:

17134581

[PubMed - indexed for MEDLINE]

Neurol Sci. 2005 Dec;26 Suppl 4:S200-3.

Intense immunosuppression followed by autologous stem cell transplantation in severe multiple sclerosis.

Capello E, Saccardi R, Murialdo A, Gualandi F, Pagliai F, Bacigalupo A, Marmont A, Uccelli A, Inglese M, Bruzzi P, Sormani MP, Cocco E, Meucci G, Massacesi L, Bertolotto A, Lugaresi A, Merelli E, Solari A, Filippi M, Mancardi GL; Italian GITMO-Neuro Intergroup on ASCT for Multiple Sclerosis.

Source

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Abstract

Aggressive forms of multiple sclerosis (MS) represent a limited group of demyelinating diseases that rapidly progress to severe disability. Currently available therapies are poorly effective against these clinical entities. Recently, it has been demonstrated that intense immunosuppression followed by autologous haematopoietic stem cell transplantation (AHSCT) can affect the clinical course of individuals with severe MS and completely abrogate the inflammatory activity detected by MRI. We report the result of the Italian phase 2 GITMO study, a multicentre study in which 21 MS patients, who were rapidly deteriorating and not responding to the usual therapeutic strategies, were treated with this procedure. The clinical effect of the treatment is long lasting, with a striking abrogation of inflammation detected by MRI findings. These results support a role for intense immunosuppression followed by ASCT as treatment in rapidly evolving MS cases unresponsive to conventional therapies.

PMID:

16388358

[PubMed - indexed for MEDLINE]

Cytotherapy. 2005;7(4):363-7.

Clinical and quality of life responses to high-dose chemotherapy plus autologous stem cell transplantation in patients with multiple sclerosis: two case reports.

Novik AA, Ionova TI, Bisaga GN, Kishtovich AV, Fedorenko DA, Ivanov RA, Gorodokin GI.

Source

Russian Cooperative Group for Cellular Therapy, Moscow, Russian Federation.

Abstract

During the last several years high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) has been established as a therapeutic option for multiple sclerosis (MS) patients. We report on the long-term effects of HDCT + ASCT in two female patients affected by secondary progressive and relapsing-remitting types of MS, respectively. As a result, disease stabilization was achieved in the first case and disease improvement in the second one. Both patients were off immunosuppressive or immunomodulating therapy throughout the post-transplant period. Notably, HDCT + ASCT resulted in an excellent quality of life (QoL) response in both cases. Our findings demonstrate that HDCT + ASCT could be considered as an effective treatment for MS patients. Moreover, QoL measurement seems to be an effective approach to assessment of treatment outcomes at long-term follow-up of patients with MS.

PMID:

16162458

[PubMed - indexed for MEDLINE]

Mult Scler. 2005 Jun;11(3):367-71.

Autologous stem cell transplantation as rescue therapy in malignant forms of multiple sclerosis.

Mancardi GL, Murialdo A, Rossi P, Gualandi F, Martino G, Marmont A, Ciceri F, Schenone A, Parodi RC, Capello E, Comi G, Uccelli A.

Source

Department of Neurosciences, Ophthalmology and Genetics, University of Genoa, Genoa, Italy.
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Abstract

Malignant forms of multiple sclerosis (MS) represent a limited group of very aggressive demyelinating diseases, which rapidly progress to severe disability leading often to life-threatening conditions. On these clinical entities, currently available therapies for MS are not very effective. Recently, it has been demonstrated that intense immunosuppression followed by autologous stem cell transplantation (ASCT) can affect the clinical course of individuals with severe MS and completely abrogate the inflammatory activity detected by magnetic resonance imaging (MRI). We report on the treatment with intense immune ablation followed by ASCT of three patients with malignant MS whose clinical course indicated a dramatically poor prognosis. This procedure succeeded in halting the rapidly worsening course of disease. The effect was long lasting, as demonstrated by a sustained efficacy over a two-year period in two subjects and 12 months in the third case. In addition, a striking effect on inflammation-related MRI findings was obtained. These results support a role for intense immunosuppression followed by ASCT as treatment in rapidly evolving malignant MS cases unresponsive to conventional therapies.

PMID:

15957523

[PubMed - indexed for MEDLINE]

Lancet Neurol. 2005 Jan;4(1):54-63.

Autologous haematopoietic-stem-cell transplantation for multiple sclerosis.

Blanco Y, Saiz A, Carreras E, Graus F.

Source

Service of Neurology, Hospital Clínic, Institut d'Investigació Biomèdica August Pi i Sunyer, University of Barcelona, Spain.

Abstract

Intense immunosuppression followed by autologous haematopoietic-stem-cell transplantation (HSCT) is being assessed as a potential treatment for patients with severe multiple sclerosis (MS). The treatment was developed from research that showed autologous HSCT was as effective as allogeneic HSCT in the treatment of experimental autoimmune encephalomyelitis. The treatment is thought to eradicate the defective immune system, and the infused haematopoietic stem cells reconstitute an immune system that is more tolerant to the nervous system. About 250 patients with MS have been treated with autologous HSCT as part of phase I and phase II open trials. Autologous HSCT seems feasible in MS and assessment with clinical and MRI measures suggests it induces a profound and long-lasting suppression of inflammation. The course of MS seems to be stabilised after autologous HSCT, especially in ambulatory patients with evidence of active disease. Autologous HSCT deserves further study in randomised controlled trials.

PMID:

15620857

[PubMed - indexed for MEDLINE]

Blood. 2005 Mar 15;105(6):2601-7. Epub 2004 Nov 16.

Autologous HSCT for severe progressive multiple sclerosis in a multicenter trial: impact on disease activity and quality of life.

Saccardi R, Mancardi GL, Solari A, Bosi A, Bruzzi P, Di Bartolomeo P, Donelli A, Filippi M, Guerrasio A, Gualandi F, La Nasa G, Murialdo A, Pagliai F, Papineschi F, Scappini B, Marmont AM.

Source

Bone Marrow Transplantation Unit, Careggi Hospital, University of Florence, Italy. r.saccardi@dac.unifi.it

Abstract

Hematopoietic stem cell transplantation (HSCT) has been proposed for the treatment of severe multiple sclerosis (MS). In a phase 2 multicenter study we selected 19 non-primary progressive MS patients showing high disease activity on the basis of both brain magnetic resonance imaging (MRI) and sustained clinical deterioration despite conventional treatments. After stem cell mobilization with cyclophosphamide (CY) and filgrastim, patients were conditioned with BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea), cytosine arabinoside, etoposide, and melphalan (BEAM) followed by antithymocyte globulin (ATG). Unmanipulated peripheral blood stem cells (PBSCs) were then infused. No maintenance treatment was administered with a median follow-up of 36 months (range, 12 to 72 months). All patients showed clinical stabilization or improvement; 3 subsequently deteriorated, 1 beyond the baseline. No MRI active lesions were detected after the HSCT except in 1 patient who showed a new lesion at 4.5 years. Infections were limited and restricted to 3 months after HSCT. Health-related quality of life was assessed through the 54-item MS quality of life (MSQOL-54) questionnaire, showing a statistically significant improvement in both composite scores and in most of the individual domains. HSCT is able to induce a prolonged clinical stabilization in severe progressive MS patients, resulting in both sustained treatment-free periods and quality of life improvement.

PMID:

15546956

[PubMed - indexed for MEDLINE]