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ORIGINAL COMMUNICATION

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Guidelines for autologous blood and marrow stem cell transplantation in multiple sclerosis:

a consensus report written on behalf of the European Group for Blood and Marrow Transplantation and the European Charcot Foundation

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Abstract Recent reports suggest the possible beneficial effects of haemopoietic stem cell transplantation (HSCT) in autoimmune diseases such as multiple sclerosis (MS). The definition of the risk/benefit ratio for such a treatment is perceived as a major issue for the neurological community worldwide. The First Consensus Conference on Bone Marrow Transplantation in Patients with Multiple Sclerosis was held in Milan, Italy on 21 February 1998. Participants from 16 European, North American, and South American countries discussed the guidelines for performing HSCT in MS. This conference was organized in order to: (a) define criteria for patient selection; (b) define transplantation procedures to maximize efficacy of the treatment and minimize its toxicity; (c) standardize patient outcome evaluation; and (d) establish an international working group to evaluate the efficacy and safety of HSCT in MS and to study the immunological changes related to HSCT in MS patients. During the meeting in Milan agreement was reached on: (a) the preparation and distribution of a consensus report on HSCT in MS and (b) the design of an open trial for an initial assessment of the safety and efficacy of HSCT in MS. The consensus reached during the meeting and the design of the clinical trial are summarized in this contribution.

Key words Multiple sclerosis · Haemopoietic stem cell transplantation · Consensus guidelines

Haemopoietic stem cell transplantation in multiple sclerosis: rationale and state of the art

Multiple sclerosis (MS) is a serious demyelinating immune-mediated disease of the central nervous system (CNS) affecting mainly young adults and leading in the majority of cases to physical and psychological impairment [18]. The social cost of this disease is enormous; in 1991 a total of $1.5 billion dollars were spent in the United States in the effort to assist MS patients. Ten years after onset about 50% of patients have a chronic progressive course [24, 25]; this proportion increases to 70% after 15 years from disease onset and to 85% after 25 years [5]. In the malignant form of the disease, affecting 1–3% of patients, ambulation is lost in few weeks or months [5, 24, 25]. Life expectancy is reduced by about 10 years compared to the age-matched normal population [5].

Both interferon (IFN) β and copolymer 1 [4, 10–12] significantly reduce disease activity in relapsing-remitting MS (RRMS); IFNβ also significantly delays the progression of disability in RRMS and secondary-progressive MS (SPMS) [7, 11]. Nevertheless these therapeutic approaches fail to achieve a satisfactory control of the disease course in most patients, and some patients do not respond at all to these treatments. Immunosuppressive treatments, which are frequently used as second-line therapy in such MS cases, have also only partial beneficial effects [5, 13].

The unsatisfactory results obtained with conventional immunosuppressive treatments in MS have been explained in part by the incomplete eradication of T and B cells reacting against neural antigens. Considering that immune cells are generated from bone marrow precursors, myeloablative therapy requires a profound immunosuppression and may lead to the destruction of all autoreactive T and B cells in MS patients [17]. The reconstitution of a "new" immune system via the haemopoietic stem cell (HSC) graft may result in a long-lasting or even persistent remission of the disease.

The HSC graft may be syngenic (from identical twin), allogenic (from an HLA-identical sibling donor), or autologous (from the patient). In principle, allotransplant seems more reasonable than autologous transplant for the treatment of autoimmune diseases because the graft-versus-host reaction contributes to eradicating the host's aberrant immune system. Moreover, the autologous graft may increase the risk of recurrence if mature autoreactive cells are reinfused, or if the dysregulation of the immune system seen in MS originates from the stem cells. However, the higher mortality with allotransplant (15–35%) than with autologous grafts (3–10%) [23], due principally to the occurrence of a graft-versus-host disease reaction, makes allotransplant an unattractive alternative for MS patients. The source of the transplant may be either bone marrow or peripheral blood stem cells, driven out of the marrow by intensive chemotherapy and/or administration of haemopoietic growth factors [23]. For autologous graft, peripheral blood stem cells offer the advantage of a faster and more complete reconstitution while bone marrow derived stem cells contain a lower number of mature T lymphocytes, including autoreactive T cells.

There is enough experimental evidence that autologous HSCT is able to prevent or induce long-lasting remission of experimental autoimmune encephalomyelitis, the animal model for MS, although some animals do relapse [9, 14]. Recurrence of relapses has been attributed both to the pre-transplantation conditioning regimen, unable to eliminate all anti-myelin reactive cells (antigen-specific cells), and to the effector/memory cells that may still be present among the transplanted cells [9, 14]. The first indications that HSCT offers an effective treatment in autoimmune diseases arose from patients undergoing HSCT for haematological or malignant disorders and who had a concomitant autoimmune disease. Autologous HSCT in patients with malignant tumours and concomitant autoimmune disease, using protocols without T cell depletion, usually leads to remission of the associated autoimmune disease, which in some cases reappears shortly after treatment [6]. However, long-term remission of autoimmune diseases following autologous HSCT has been observed [2, 22].

In the few reported cases in which the autoimmune disease associated with lymphoma/leukaemia was MS [19], stabilization or even a tendency of improvement in the disease after autologous HSCT was observed. In a recently published open observational study of 15 patients with definite MS, a progressive course and moderate/high disability (Extended Disability Status Score, EDSS, 5–7.5), HSCT showed some adverse effects, but none lethal [8]. Moreover, durable neurological improvements have been detected on both the EDSS (7 of 15 patients) and Scripps' Neurological Rating Scale (SNRS [21]; all 15 patients) while one patient worsened at 3 months and two relapsed [8]. These preliminary results are very encouraging, but follow-up duration, ranging from 1 to 2 years, is too short to allow definite conclusions on the efficacy of the treatment. Another study on HSCT in MS patients has recently been published [3]. Three patients with definite MS, a worsening of their EDSS by 1.5 points over the 12 months preceding enrolment, and an EDSS score of 8.0 at the time of enrolment, were treated by HSCT using a conditioning regimen of cyclophosphamide, methylprednisolone and total body irradiation. Despite withdrawal of all immunosuppressive medications, functional improvement was observed in all three patients, although no significant changes in EDSS or SNRS were evident at this time. There are also other anecdotal reports at meetings and congresses of single MS patients undergoing HSCT, but, again, these are too few to allow definitive conclusions on HSCT efficacy in MS.

According to the European Group for Blood and Marrow Transplantation (EBMT) Central Registry, 42 MS patients had received transplants by October 1998. These patients' characteristics are reported in Table 1, and a short

summary of the available results is given in Table 2. Three patients died 20, 58 and 7 days after the graft; the causes of death were pneumonia, brain and lung aspergillosis, and cardiac arrest. Serious adverse events during mobilization occurred in about 30 % of patients; the most frequent were allergy, fever, infections, anaemia, and thrombosis. Transplant-related complications were extremely frequent, including allergy, bacteraemia, oral toxicity, and transitory deterioration in neurological conditions. Of the 37 patients with more than 6 months of follow-up (mean 18 months, range 6–38) 30 (82 %) improved or stabilized after the treatment. In evaluating these data, however, we must bear in mind the possibility that – although the EBMT registry should be comprehensive – publication bias towards positive results may influence the reported results.

Thus it is clear that we need to evaluate more extensively the efficacy of autologous HSCT in MS before proposing HSCT as a possible treatment for MS. We must clearly define the criteria for patient selection and those for HSCT procedures, the main issue being the risk/benefit ratio. Considering that prognostic factors are not fully satisfactory in definite MS, and that it would be worthwhile to select patients in good general condition to minimize the risks associated with the treatment, the ideal MS patient for HSCT would be one in good general condition, with moderate disability, but at high risk of rapid and irreversible deterioration in neurological symptoms.

Table 1 Characteristics of the HSCT-treated MS patients registered in the EULAR/EBMT database by October 1998 (*n*=42)

Patients characteristics	*n*
Male/female	16/26
Age (years)[a]	
< 30	9
30–39	12
40–50	16
> 50	5
Disease type	
Secondary progressive	27
Primary progressive	11
Progressive-relapsing	4
EDSS[b]	
< 5.5	7
5.5–6.0	12
6.5–7.0	13
> 7.0	3
Follow-up[c]	
1 year	20
1–2 years	10
> 2 years	9
Death	3

[a] Median 43, range 22–58)
[b] Median 6, range 4.5–8.5
[c] Median 9, range 2–39

Table 2 Preliminary results on efficacy of HSCT in MS patients registered in the EULAR/EBMT database to September 1998

Patients characteristics	*n*	%
Too early to evaluate	5	
Improvement or stabilization	30	
Signs of progression	4	
Relapses without progression	4	
Improved on EDSS	12	
Worsened on EDSS	3	
Progression-free survival[a]		85
Cumulative risk of progression		17

[a] Calculated at 38 months after HSCT

Consensus on further evaluation of HSCT in MS

The First Consensus Conference on Bone Marrow Transplantation in Patients with Multiple Sclerosis was held in Milan, Italy, on 21 February 1998. Participants from 16 European, North American and South American countries discussed the guidelines for performing HSCT in MS. The participants at the Consensus Meeting reached an agreement on the criteria for selecting patients to be transplanted and on the transplantation procedures. Moreover, it was decided that a Working Group operating under the auspices of the EBMT and the European Charcot Foundation would begin a cooperation with national and international scientific societies to produce a study protocol for an international multicentre-controlled trial.

The efficacy and safety of HSCT in MS can be determined only with a controlled prospective comparative phase III trial. However, the organization of such a trial will require a long time since important ethical, technical, economic and practical problems must first be solved.

It has been decided to perform an open multicentre, multinational, uncontrolled trial (a) to evaluate the efficacy and safety of HSCT in MS and (b) to study the HSCT effects on the immune system of MS patients. Centres participating in this trial will use a common set of criteria for selecting patients and assessing efficacy and safety, although slight variability will be allowed between centres regarding transplantation procedures.

Patient selection

The following inclusion and exclusion criteria are based on the consensus reached by the participants at the conference. These criteria are suggested for MS patients undergoing HSCT regardless of whether they are participating in the open multicentre uncontrolled study of the HSCT-MS Working Group. The basic concept is that HSCT should be undertaken before widespread irreversible white matter changes occur. MS patients with long-lasting disability

have been shown to be poor responders to HSCT [8] due to irreversibility of chronic lesions.

Inclusion criteria

- Clinically definite MS according to the Poser et al. [20] criteria
- Relapsing-remitting, secondary-progressive, progressive relapsing courses [16]
- Brain magnetic resonance imaging (MRI) findings typical of MS according to the Barkhof et al. criteria [1]
- Age between 18 and 55 years
- Disease duration ≥1 year
- EDSS between 3.0 and 6.5
- Disability progression sustained for at least 6 months in the previous 2 years of:
- ≥1.5 points if entry EDSS between 3.0 and 5.0
- ≥1.0 point if entry EDSS ≥5.5
- Clinical or MRI activity in the previous year
- Unsatisfactory response to other available therapies (based on clinical judgement)
- Informed consent

Exclusion criteria

- Pregnancy
- Concomitant severe diseases (respiratory, renal, liver, cardiac failures, psychiatric disorders, neoplasms)
- Recurrent urinary, pulmonary infections
- Previous treatments with total lymphoid irradiation or total body irradiation
- Treatment with immunosuppressive agents in the 3 months prior to study enrolment
- Treatment with IFNβ, copolymer 1 or i. v. immunoglobulins in the month preceding enrolment
- Relapse in the month preceding enrolment
- Poor compliance of the patient

Transplantation procedure

Considering the high mortality of allotransplantation, the only form of HSCT presently feasible for MS patients is autologous. Peripheral blood is generally the preferred source of stem cells, due to the short duration of aplasia, resulting in less morbidity and mortality. The procedure should be performed in an accredited bone marrow transplantation unit.

Stem cell mobilization and purging

1. When mobilization is performed, granulocyte colony-stimulating factor (10 mg/kg daily) alone can be used once daily or following a priming dose of 2 g/m^2 cyclophosphamide. Ex vivo T-cell depletion is not mandatory provided that antithymocyte globulin treatment is used after stem cell infusion, but it is recommended considering the potential of reinfusing autoimmune T cells along with the autologous HSCT, although studies performed with [8] or without [3] T cell purging have shown similar results. Very intense T-cell depletion increases the risk of infections.

Conditioning and infusion of stem cells

1. Ablation of the MS patients' autoaggressive immune system is the main goal of the conditioning protocol. Three conditioning regimens, all traditionally used in blood or marrow transplants, are suggested:
   - Cyclophosphamide 60 mg/kg for 2 days at 1-h i. v. infusion followed by total body irradiation as currently used at the treating centre
   - Busulphan 1 mg/kg every 6 h for 4 days; total 16 mg/kg followed by cyclophosphamide 60 mg/kg for 2 days
   - Carmustine, etoposide, cytosine arabinoside, melphalan protocol, based on the administration of the following drugs (day 0=day of HSCT): carmustine 300 mg/m^2 i. v. (day –6 before HSCT), etoposide 200 mg/m^2 i. v. (days –5, –4, –3 and –2), cytosine arabinoside 200 mg/m^2 once a day i. v. (days –5, –4, –3 and –2), and melphalan 140 mg/m^2 i. v. (day –1).

   On day 0, stem cells are thawed and infused. The number of CD34$^+$ to be reinfused should not be less than 2x10^6/kg body weight (when T-cell purging is performed 1x10^5 T cells/kg body weight of cells should be achieved). The patients predisposed to developing allergic reactions may suffer from serious reaction such as hypotension. Preventive treatment with hydrocortisone, pethidine, promethazine, paracetamol and ondansetron can be administered before stem cell infusion.
2. Antithymocyte globulins (10 mg/kg for thymoglobulin Merieux or 60 mg/kg for Atgam, Upjohn) should be given along with Methyl-Prednisolone 0.5 g/day on days +1 and +2 after stem cell infusion. The administration of antithymocyte globulins is mandatory if T-cell purging has not been performed. Immunoglobulins (0.5 g/kg b. w.) can be administered i. v. as supportive therapy on days +7, +8, +23 and +38. To prevent infections oral ciprofloxacin, fluconazole and acyclovir are given although each individual centre must decide independently which kind of prophylaxis to use.

Treatment toxicity

Regular surveillance must be maintained during hospitalization for stem cell mobilization and for transplantation.

Adverse experiences should be recorded according to the World Health Organization grading system. Special attention should be given to the nervous system to evaluate toxicity of the treatment on the nervous system itself, which could aggravate MS and determinate the appearance of new symptoms.

Safety and efficacy monitoring

The design of the study is based both on the minimization of risks and on long-term clinically relevant outcomes. An external safety committee will monitor the study, analysing serially the data on every ten patients included. The trial will be stopped at any time if any of the following criteria is reached:

- HSCT-related death ≥15 %
- Clinical or MRI activity ≥50 %
- Confirmed disability progression ≥30 %
- HSCT related death + confirmed progression ≥30 %

Clinical activity is defined as the occurrence of a relapse with sequelae confirmed 6 months later while MRI activity is defined as the presence of one or more active lesions. The definition of confirmed progression is: deterioration ≥1.0 EDSS point if EDSS at entry is ≥3.5 and ≤5 or deterioration ≥0.5 EDSS points if EDSS at entry is ≥5.5. The progression must be sustained for at least 6 months.

To balance the weakness of an open trial design the primary endpoint of the study should be as objective as possible and highly relevant from a clinical point of view. Moreover, because HSCT is a one-shot therapy, long-term efficacy must be demonstrated. Either an HSCT-related death or a confirmed progression 3 years after treatment can reasonably be considered a treatment failure. A death should be considered as HSCT related if it occurs within 3 months from the start of conditioning. Meta-analysis of the placebo groups in trials enrolling MS patients with a progressive form of the disease which underwent the same evaluation as that which we propose revealed a proportion of disability progression between 21.9 % and 59.4 % in follow-up periods ranging between 1.8 and 3.6 years. These figures may be lower using more conservative definitions of confirmed progression [26]. Thus we propose to consider the HSCT as effective only if the rate of treatment failure at 3 years is less than 20 %. This means that 80 % of the patients undergoing treatment should not have a confirmed progression or a HSCT-related death after the treatment. The decision to use a definition of confirmed progression of high sensitivity but low specificity reflects the importance of not underestimating the progression rate in MS patients undergoing HSCT. Moreover, the follow-up duration of 3 years is mandatory to assess properly whether putative HSCT effects in MS are reversible. An interim analysis based on safety and efficacy parameters will be performed when 30 patients complete 18 months of follow-up.

The following primary and secondary end-points are indicated for the open multicentre uncontrolled study:

Primary end-points

- Confirmed progression (≥1.0 EDSS point if initial EDSS ≤5 or ≥0.5 EDSS point if initial EDSS ≥5.5 sustained for at least 6 months)
- HSCT-related death

Secondary end-points

- Progression of impairment (≥10 SNRS points sustained for at least 6 months)
- Relapse rate
- Brain MRI findings:
- Number of enhancing lesions on post-contrast T1-weighted scans
- Total lesion volume on T2-weighted scans

Assessments

A long-term follow-up is mandatory for the assessment of both efficacy and adverse events of HSCT in MS in both single patients and patients enrolled in the clinical trial of the HSCT-MS Working Group. The trial must have a follow-up of at least 3 years. The following assessment schedule is mandatory for patients enrolled in this trial, but it is also recommended for single patient's treatments and pilot studies.

Neurological evaluation

- To be performed at the time of patient entry (before conditioning), before HSCT, 1 month and every 3 months after HSCT for the next 3 years; the examination should be recorded by video and assessed by an independent physician:
- Functional systems, EDSS [15], SNRS [21], ambulation index, 9-hole peg test

Adverse events

- To be performed at the time of patient entry, before HSCT, 1 month later and every 6 months for the next 3 years:
- Evaluation of safety parameters: blood tests, liver and renal functions, chest X-ray, electrocardiogram

Immunological/haematological evaluation

a: Basic evaluations

- To be performed at the time of patient enrolment, before HSCT, 1 month later and every 6 months for the next 3 years:
  - Blood count, renal and liver functions
  - Blood cell phenotype (CD3, CD4, CD8, CD14, CD19, CD45RA/RO, CD56)
  - Circulating autoantibodies (e. g. anti-nuclear antibodies)
  - Ig (A, G, M) serum levels
- To be performed at the time of patient enrolment and 3 years after HSCT
  - CSF/serum oligoclonal bands
  - IgG indices (Link, Reiber-Felgenhauer, Tourtellotte)
- To be performed at the time of patient enrolment and every year after HSCT
  - Circulating antibodies against common infectious agents (cytomegalovirus, Epstein-Barr virus, rubella, toxo, herpes simplex virus, herpes zoster varicellosus, hepatitis B and C viruses, human immunodeficiency virus, pneumococci, tetanus)

b: Optional evaluations

- To be performed at the time of patient enrolment and every 6–12 months after HSCT
  - Delayed-type hypersensitivity against tuberculin and *Candida*
  - Cytokine production of the circulating lymphocytes (IFNγ, interleukin–4, interleukin–10, transforming growth factor-β, tumor necrosis factor-α)
  - Proliferation activity of circulating lymphocytes against myelin antigens (myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein)
- To be performed at the time of patient enrolment and 3 years after HSCT
  - Blood T-cell receptor-β spectrotype

Brain MRI

- To be performed at entry, before HSCT, 1 month after HSCT and thereafter every 6 months during the 3 years follow-up
  - Brain MRI examination will include pre- and post-contrast T1- weighted sequences, T2-weighted sequences, magnetization transfer sequences (where available). The following MRI items should be measured: number of brain MRI active lesions (new and enlarging T2 plus enhancing lesions); number of active scans; T1 lesion volume; T2 lesion volume; brain atrophy (if available); magnetization transfer ratio histogram (if available).

Conclusions

At present, HSCT is an emerging treatment option in MS. It must be used with extreme caution due to its high risk of mortality. The autologous procedure is presently preferred due to the unacceptably high risks of allotransplantation. In the framework of the criteria presented above, indication for treatment remains the responsibility of the treating neurologist and the patient. To assess the risk/benefit ratio of autologous HSCT in MS it is mandatory to collect further data. Due to the limited number of patients that can be treated in single centres, international cooperation is needed. The First Consensus Conference on Bone Marrow Transplantation in Patients with Multiple Sclerosis reached a consensus to conduct an open trial to recruit sufficient MS patients for an initial investigation of the efficacy and safety of HSCT in MS. Based on the results of this open trial the possibility of performing a large phase III controlled study will be evaluated. All centres participating in the trial agreed to include and follow patients according to the above guidelines. All the data regarding patient characteristics and the HSCT procedure adopted will be reported on standardized forms to the International Autoimmune Disease Stem Cell Project database located in Basel, Switzerland.

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References

1. Barkhof F, Filippi M, Miller DH, Scheltens P, Campi A, Polman CH, Comi G, Ader HJ, Losseff N, Valk J (1997) Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain 120:2059–2069
2. Blank M, Krause I, Lanir N, Vardi P, Gilburd B, Tincani A, Tomer Y, Shoenfeld Y (1995) Transfer of experimental antiphospholipid syndrome by bone marrow transplantation. The importance of T cells. Arthritis Rheum 38:115–122
3. Burt RK, Traynor AE, Cohen B, Karlin KH, Davis FA, Stefoski D, Terry C, Lobeck L, Russell EJ, Goolsby C, Rosen S, Gordon LI, Keever-Taylor C, Brush M, Fishman M, Burns WH (1998) T cell-depleted autologous hematopoietic stem cell transplantation for multiple sclerosis – report on the first three patients. Bone Marrow Transpl 21:537–541
4. Comi G, Filippi M, for the Copaxone MRI Study Group (1999) The effect of glatiramer acetate (Copaxone®) on disease activity as measured by cerebral MRI in patients with relapsing-remitting multiple sclerosis (RRMS): a multi-center, randomized, double-blind, placebo-controlled study extended by open-label treatment. Neurology 52:A289
5. Compston A, Ebers G, Lassmann H, McDonald I, Matthews B, Wekerle H (1998) McAlpine's multiple sclerosis, 3rd edn. Churchill Livingstone, Edinburgh
6. Euler HH, Marmont AM, Bacigalupo A, Fastenrath S, Dreger P, Hoffknecht M, Zander AR, Schalke B, Hahn U, Haas R, Schmitz N (1996) Early recurrence or persistence of autoimmune diseases after unmanipulated autologous stem cell transplantation. Blood 88:3621–3625
7. European Study Group on Interferon beta–1b in Secondary Progressive MS (1998) Placebo-controlled multicentre randomised trial of interferon beta–1b in treatment of secondary progressive multiple sclerosis. Lancet 352:1491–1497
8. Fassas A, Anagnostopoulos A, Kazis A, Kapinas K, Sakellari I, Kimiskidis V, Tsompanakou A (1997) Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: first results of a pilot study. Bone Marrow Transpl 20:631–638
9. Gelder M van, Bekkum DW van (1996) Effective treatment of relapsing experimental autoimmune encephalomyelitis with pseudoautologous bone marrow transplantation. Bone Marrow Transpl 18:1029–1034
10. IFNB Multiple Sclerosis Study Group (1993) Interferon beta–1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 43:655–661
11. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Fischer JS, Goodkin DE, Granger CV, Simon JH, Alam JJ, Bartoszak DM, Bourdette DN, Braiman J, Brownscheidle CM, Coats ME, Cohan SL, Dougherty DS, Kinkel RP, Mass MK, Munschauer FE 3rd, Priore RL, Pullicino PM, Scherokman BJ, Whitham RH, et al. (1996) Intramuscular interferon beta–1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol 39:285–294
12. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, Myers LW, Panitch HS, Rose JW, Schiffer RB (1995) Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. Neurology 45:1268–1276
13. Kappos L (1997) Therapy. In: Kesselring J, McDonald WI (eds) Multiple sclerosis. Cambridge University Press, Boston, pp 148–167
14. Karussis DM, Slavin S, Lehmann D, Mizrachi-Koll R, Abramsky O, Ben-Nun A (1992) Prevention of experimental autoimmune encephalomyelitis and induction of tolerance with acute immunosuppression followed by syngenic bone marrow transplantation. J Immunol 148:1693–1698
15. Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33:1444–1452
16. Lublin FD, Reingold SC (1996) Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 46:907–911
17. Marmont AM, Tyndall A, Gratwohl A, Vischer T (1995) Haemopoietic precursor-cell transplants for autoimmune diseases. Lancet 345:978
18. Martin R, McFarland HF, McFarlin DE (1992) Immunological aspects of demyelinating diseases. Annu Rev Immunol 10:153–187
19. McAllister LD, Beatty PG, Rose J (1997) Allogeneic bone marrow transplant for chronic myelogenous leukemia in a patient with multiple sclerosis. Bone Marrow Transpl 19:395–397
20. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 13:227–231
21. Sipe JC, Knobler RL, Braheny SL, Rice GP, Panitch HS, Oldstone MB (1984) A neurologic rating scale (SNRS) for use in multiple sclerosis. Neurology 34:1368–1372
22. Snowden JA, Kearney P, Kearney A, Cooley HM, Grigg A, Jacobs P, Bergman J, Brooks PM, Biggs JC (1998) Long-term outcome of autoimmune disease following allogeneic bone marrow transplantation. Arthritis Rheum 41:453–459
23. Tyndall A, Gratwohl A (1997) Blood and marrow stem cell transplants in auto-immune disease: a consensus report written on behalf of the European League Against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transpl 19:643–645
24. Weinshenker BG (1995) The natural history of multiple sclerosis. Neurol Clin 3:119–146
25. Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, Ebers GC (1989) The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain 112:133–146
26. Weinshenker BG, Issa M, Baskerville J (1996) Meta-analysis of the placebo-treated groups in clinical trials of progressive MS. Neurology 46:1613–1619