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Patti Mandalfino
George Rice
Anne Smith
Jay L. Klein
Linea Rystedt
George C. Ebers

Bone marrow transplantation in multiple sclerosis

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P. Mandalfino · G. Rice
Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada

A. Smith
From the Department of Medical Oncology, University of Western Ontario, London, Ontario, Canada

J. L. Klein
Division of Haematology Oncology, Department of Internal Medicine, Karamanos Cancer Institute, Wayne State University, Detroit, Mich., USA

L. Rystedt
Division of Endocrinology and Metabolism, Wayne State University, Detroit, Mich., USA

G. C. Ebers (✉)
Department of Clinical Neurology, University of Oxford, Radcliffe Infirmary, Woodstock Road, Oxford, OX2 6HE, UK
Tel.: +44–1865–228579,
Fax: +44–1865–790493,
e-mail: george.ebers@clneuro.ox.ac.uk,

Abstract There is strong circumstantial evidence that multiple sclerosis (MS) is an autoimmune disease. Nonspecific immunosuppressive therapy has not been successful in altering the natural course of the illness. Bone marrow transplantation has heretofore been a radical therapy used in patients with life-threatening malignancies but has potential as a treatment for human autoimmunity. In MS there have been no controlled studies. We report here four patients with MS undergoing bone marrow transplantation with 6–48 months of follow-up. In three this was carried out for co-existing malignancy and in one as an experimental treatment for MS using the patient's unaffected identical twin as a donor. The limited outcome that can be evaluated in these patients supports further experimentation into this treatment modality in MS patients with poor prognostic indications.

Key words Multiple sclerosis · Bone marrow transplantation · Outcome

Introduction

There is good circumstantial evidence that multiple sclerosis (MS) is an autoimmune disorder [11]. The mechanisms by which autoimmunity develops and the pathways of tissue injury have not been fully elucidated, but T-cell mediated pathways are thought to play a central role. The success of nonspecific immunosuppression in reducing transplantation rejection, where pathology is demonstrably T-cell mediated in preventing the emergence of spontaneous autoimmune disease in experimental animals, and in treating some human autoimmune disorders, has led to extensive trials of nonspecific immunosuppressive drugs in the treatment of MS. These studies have been disappointing perhaps because sufficient suppression to impair secondary immune responses cannot be achieved without substantial morbidity [12]. Recently a number of studies have achieved marked and prolonged reduction in lymphocyte counts to levels seen in patients with human immunodeficiency virus infection, without materially slowing the progression of disease [2, 13, 15]. These results should engender some doubt as to the likelihood of future success with this general approach.

Given these considerations, and because insufficient understanding makes current prospects for antigen-specific immunosuppression appear bleak, attention has turned to other measures with potential to slow activity in patients with aggressive disease.

Dramatic developments in the treatment of malignant disease have lowered the morbidity and mortality of bone marrow transplantation (BMT) to a level which now warrants evaluation as a potential treatment for human autoimmune disease with poor expected outcome. To date, there have been no systematic studies of this treatment modality and the current approaches are hermeneutic.

These are largely based on anecdotal reports of patients having organ specific autoimmune diseases who received BMT for co-existent malignancy. This evidence has led to a small number of highly selected patients to date who have received BMT specifically for autoimmune disease. Only early results are available, and discussion with respect to entry criteria, transplantation protocols, and methods of evaluation are in relatively early stages [14]. However, there is support for this approach in a variety of spontaneous animal models of autoimmunity where various methods of BMT have been successful [14].

The most studied animal model for MS is experimental allergic encephalomyelitis, but, in contrast to lupus, arthritis and juvenile diabetes, there is no spontaneous animal model of MS. It can be arrested by syngeneic, allogeneic and autologous BMT; however, these studies must be interpreted in the context of a very large number of seemingly unrelated manipulations which are similarly successful [12]. In MS only a single large series of patients has been published to date, but outcomes are very short-term, extending only to 12 months post-BMT, with median of only 6 months [5].

We report our experience with BMT in the four MS patients who have received BMT among the 4500 patients seen at the MS Clinic, University of Western Ontario. The results reported here support other anecdotal evidence suggesting that this may be an effective treatment option in patients where expected outcome justifies some mortality and morbidity, although outcome data to date remain limited.

Case reports

Patient 1

The patient was a woman who was diagnosed with MS at the age of 47 years (Table 1). Her initial symptom had occurred 4 years earlier when she developed 2 weeks of ataxia, which resolved. In the 9 months prior to her diagnosis she had a gradual onset of four-limb ataxia and weakness as well as dysarthria and urinary urgency. Examination at time of presentation showed visual acuity 20/100 o. d. and 20/70 o. s., bilateral internuclear ophthalmoplegias, upbeat nystagmus, brisk reflexes, extensor plantar responses, and severe gait ataxia. Her Extended Disability Status Score (EDSS) had reached 6.5 in the 4 years since clinical onset. Magnetic resonance imaging (MRI) of the head was consistent with MS. Her course was actively progressive and complicated by cognitive deterioration. She was diagnosed with acute lymphoblastic leukaemia (ALL) 21 months after her MS diagnosis.

Autologous BMT for ALL was undertaken because of lack of HLA-matched allogeneic donor. Induction/consolidation chemotherapy included doxorubicin, vincristine, prednisone, cytarabine and teniposide. Maintenance chemotherapy included doxorubicin, 6-mercerptopurine and prednisone. The immediate post-BMT period was uncomplicated, but her ALL relapsed 3 months later. She was admitted for a second course of remission induction chemotherapy and developed *Pseudomonas* sepsis that resulted in death. Her MS symptoms had been stable since her ALL diagnosis to the point of her death 6 months post-BMT. At post-mortem examination, sections through the brain showed two areas consistent with acute demyelinating plaques. However, re-examination of these areas

Table 1 Summary of patient outcomes

	Patient 1	Patient 2	Patient 3	Patient 4
Age of MS onset (years)	43	47	43	35
Sex	Female	Female	Male	Female
Disease subtype	Secondary progressive	Secondary progressive	Relapsing progressive	Primary-progressive
Disease activity prior to transplant	Increase in EDSS from 4.0 to 6.5 in 24 months prior to transplant	prior to transplant stable at EDSS 1.0	stable at EDSS 1.0 for 2 years prior to transplant	Two relapses per year; increase in EDSS from 3.5 to 6.5 in 48 months prior to transplant
Indication for transplantation	Acute lymphocytic leukaemia	Small cell lymphoma	Acute myelogenous leukaemia	MS
Type of transplantation	Autologous	Autologous	Allogenic	Syngeneic from identical twin
EDSS at transplantation	6.5	1.5	1.0	6.5
EDSS at last visit	Died 6 months after transplant; EDSS remained at 6.5 to time of death	Died 40 months after transplant; MS stable to time of death	1.0 (48 months after transplant)	6.5 (26 months after transplant)

showed that the perivascular infiltrate was secondary to the known septicaemia and not consistent with acute demyelination (H. Lassman, personal communication).

Patient 2

This woman presented at the age of 51 years with an episode of left optic neuritis (Table 1). Previous neurological history included resolving episodes of bilateral lower extremity paraesthesia, bilateral hand numbness and left upper extremity clumsiness. Her examination showed colour desaturation in the left eye, mild left-sided pyramidal findings, and vibratory impairment in the lower extremities yielding an EDSS score of 1.5. MRI of the head was supportive of MS. The patient entered a sulfasalazine trial and had follow-up examinations at 5 months and 8 months after her initial presentation in which her MS was stable and her EDSS score remained unchanged. However, 9 months after initial presentation she developed right facial swelling. A biopsy specimen of her right maxillary sinus revealed a small cell lymphoma. She was discontinued from the trial. She began a series of cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy and entered a clinical remission. However, she then developed a soft palate mass, and biopsy revealed recurrence of her lymphoma. A second series of the above chemotherapy was instituted. Her malignancy became quite refractory to chemotherapy, which included further courses of dexamethasone, cytarabine and cisplatin, as well as carmustine, etoposide, cytosine arabinoside and melphalan. Autologous BMT was undertaken. Stem cells were harvested after granulocyte colony stimulating factor, and she was conditioned with etoposide and melphalan. The immediate post-BMT period was complicated with esophagitis and pneumonia. Seven months later her disease recurred, requiring more chemotherapy as well as palliative radiotherapy to her upper extremity nodes. Finally the patient developed partial bowel obstruction and was found on rectal examination to have a large tumour biopsy proven to be recurrent lymphoma. Palliative treatment was initiated, and she died 2 months later. The patient survived 40 months after her initial diagnosis of MS and 16 months after her autologous BMT. Clinically the patient's MS symptoms had remained stable, with no evidence of disease exacerbation during or following BMT.

Patient 3

This patient was 43 years old when he presented complaining of left-handed numbness (Table 1). No other neurological problems were reported. Examination was significant for impaired vibratory perception in the left hand and both lower extremities, and up going toes bilaterally giving a composite EDSS of 1.5. MRI of the brain showed areas of increased signal periventricularly and subcortically consistent with MS. Fourteen months later he developed Lhermitte's phenomenon. Two years after his MS diagnosis he developed acute myelogenous leukaemia. He had six courses of induction chemotherapy with mitoxantrone and cytarabine, complicated by fungal pneumonia and febrile neutropenia. The patient underwent an allogeneic BMT from an HLA-matched sibling. He was prepared for transplantation with busulfan and cyclophosphamide. The post-BMT course was complicated by minor cutaneous graft-versus-host disease. The patient also developed varicella, an infection which both he and his sibling donor had had in earlier childhood. His transplantation was otherwise uncomplicated. His MS symptoms have remained stable throughout his haematological illness and in the post-BMT period, which is now 48 months later. His last EDSS score of 1.0 was based on the isolated finding of bilateral up-going toes. He has had repeat MRI after BMT which showed no change from the previous pre-transplantation examination in 1992 (scans available on request).

Patient 4

The patient is a 48-year-old woman who presented originally at the age of 35 years with a history of thoracic band-like sensation (Table 1). She had had an episode of diplopia 2 years earlier, and the year prior to presentation she had experienced an episode of left-handed numbness. Physical examination showed nystagmus, mild dysarthria, mild pyramidal signs in the lower extremities and gait ataxia. MRI was supportive of MS. The patient continued to have active MS symptoms suffering approximately two attacks per year with gradual accumulation of disability. Her EDSS score was 2.0 at presentation, 5.0 8 years later and 6.5 10 years after diagnosis. The patient had an identical twin and wished to proceed with experimental syngeneic BMT from her unaffected twin. Screening of her twin clinically and by MRI showed no evidence of MS. The patient underwent BMT at Wayne State University (Michigan, USA). Conditioning was carried out with cyclophosphamide and total body irradiation. Her twin's stem cells were harvested after granulocyte colony stimulating factor. The post-BMT period was complicated by urinary tract infection requiring intravenous antibiotic treatment. Her MS symptoms were not exacerbated at that time. She has enjoyed stability from her MS and remains with an EDSS score of 6.5 26 months post-transplantation. The patient has had one MRI since the transplantation procedure, which showed no change from the pre-transplantation MRI. Follow-up CSF examination showed no evidence of oligoclonal bands which had been present pre-transplantation.

Discussion

We report four patients who are the only patients with MS, to our knowledge, who have undergone BMT in an MS Clinic where some 4500 patients have been seen since 1972. Two of these patients succumbed to their malignancy and/or septic complications after a short period of follow-up. MS symptoms were stable throughout the transplantation and follow-up in these individuals. The other two have remained stable for 26 and 48 months after the transplantation. These data are insufficient to draw any confident conclusions. However, these results cannot be viewed as discouraging. For example, patient 4 had an EDSS score of 6.5 in 1996 at the time of transplantation. No more treatment effect than apparent stabilization can be reasonably expected and now close to 26 months post-transplantation this has occurred. However, natural history data have shown that the average patient spends 4.24 years at EDSS 6 level (D. M. Wingerchuk and G. C. Ebers, unpublished data). Similarly, while patient 3 has remained clinically stable at an EDSS score of 1.0 48 months post-transplantation, he had been stable at the same level for 2 years prior to the transplantation. It is encouraging that post-transplantation MRI shows no accumulation of lesions compared to pre-transplantation in the two surviving patients. Finally, oligoclonal banding which was present in one patient pre-transplantation can no longer be detected post-transplantation.

These results are consistent with a recent report of 15 patients with progressive MS and entry EDSS scores of 5–7.5 who underwent autologous blood stem cell transplantation [5]. They were conditioned with carmustine, etoposide, cytosine arabinoside and melphalan and with anti-thymocyte globulin. Of the 15 patients 7 improved by at least 1 point on the EDSS scale, and 4 improved by 1.5 points or more. Of those who did not improve on the EDSS score, all but one remained stable 6–12 months after stem cell transplantation. However, median follow-up at time of publication was only 6 months, and although encouraging, it was too early to draw definite conclusions.

The need for long-term follow-up cannot be overstated. Patients with MS develop disability gradually over the course of years, and therefore stability of several months' or even years' duration cannot be assumed to represent a meaningful effect. Stabilization in these patients to date may be due to the profound immunosuppression which occurs in the context of transplantation. After BMT, patients are functionally immunocompromised and show inverted CD4/CD8 ratios for up to 24 months [6]. Only beneficial effects of transplantation enduring after a period of prolonged relative immunosuppression would support an effect independent of the intensive immunosuppression. Several reported cases of relapse following autologous BMT procedures reinforce the concern that short-term benefit does result from immunosuppression, and that autoreactive T-cells either have not been eradicated or have reemerged as part of the developing donor T-cell repertoire [4]. The demonstration of the mechanism involved could have major significance for our understanding of MS.

Designing patient selection criteria for autoimmune diseases such as MS presents some disease-specific challenges. Most significant is the fact that the disease has a highly variable outcome ranging from benign to highly malignant. Predicting those destined for the most malignant outcome early in the disease has obvious value both in this context and in the general context of potential therapies entailing risk. Inclusion criteria for BMT have been suggested, such as EDSS greater than or equal to 5.0 and a 1-point deterioration in the year preceding the transplantation. However, patients at the high end of the disability scale are at greater risks for complication and therefore increase the "risk side" of the risk-benefit ratio. Indwelling catheters and reduced lung function secondary to immobility probably entail increased susceptibility to serious infection. Ideally, we would like to be able to identify those patients who are at risk for the worst outcome, the so-called severe autoimmune diseases, prior to development of significant disability to optimize risk-benefit ratio. Using the clinical disease activity in the year preceding transplantation may be short-sighted because of the lack of evidence that disease behaviour in the preceding short term reliably predicts overall disease outcome. For example, patients selected for a drop of 1 point in the EDSS in the year prior to entering a clinical trial showed stabilization rates of 75–85 % after 1 year, demonstrating the well-recognized phenomenon of regression towards the mean [19].

In our own population we have amassed a natural history database on more than a 1000 patients which now extends beyond 25 years of observation. Longitudinal analysis of the data provides some reasonable prognostications which we believe agree well with empirical observations [3]. These data provide the opportunity for individual specific prognosis. Although only probability can be given, they may be helpful for both patient selection and for informed consent. For example, if a patient with relapsing-remitting disease has five or more attacks in the first 2 years of the illness, and reaches an EDSS 3 level in 2 years or less, there is a 94.74 % chance (95 % confidence intervals, 85–100 %) of the patient reaching an EDSS 6 level within the ensuing 7 years. For primary-progressive patients who reach an EDSS 6 level in 3 years or less the probability of becoming permanently wheelchair bound within 10 years of disease onset is 79.5 % (95 % confidence intervals 67.6–100 %).

These predictors can provide easily understood probabilities to enhance informed decisions and consent and avoid the known underestimations by patients with potentially serious disease. There will not be unanimity as whether 5–8 % mortality risk is justified to potentially avoid an 80 % chance of becoming permanently wheelchair bound within 10 years. Risks may be lower in selected centres, but where information is not available, morbidity from pooled published data should suffice. Our

preliminary results indicate that patients view risk differently depending on their life circumstances, their experience with MS and their personality type, this being either risk-taking or risk-adverse. In any case, investigators are obligated to ensure that the risk-benefit ratio is optimized. Available natural history data have potential to predict with reasonable confidence patients destined for a bad outcome before significant irreversible disability. This may make possible the use of BMT to maximum benefit.

The methodology for BMT may prove to be very important, and definitive approaches can only be developed through a systematic approach to the data. A major advantage of autologous vs. allogenic BMT is the lower risk. Autologous BMT has about a 5 % mortality risk, which is considerably better than allogeneic BMT in which the mortality rate is approximately 15–20 % [1]. Autologous BMT also avoids risk of graft-versus-host disease, which is the major contributor to morbidity and mortality after allogeneic BMT. However, the fear with autologous BMT is the potential to recapitulate auto reactive T-cells. Animal models have shown rats with experimental allergic encephalomyelitis to have substantially higher spontaneous and induced relapse rates in the autologous versus allogeneic BMT situation [9]. Human data have also demonstrated a tendency to relapse [4]. Despite this, autologous BMT is presently considered the transplantation method of choice in autoimmune diseases (except in the case of identical unaffected twin where syngeneic BMT is possible) because of its more acceptable levels of morbidity and mortality. T-cell purging of the autologous graft is used to reduce the risk of disease relapse by removing potentially auto reactive T-cells from the graft.

No consensus exists regarding conditioning for the procedure. Animal data suggest that total body irradiation (TBI) is necessary to ablate the diseased immune system [8]. TBI has the disadvantage of an increased risk of late malignancies [17]. Additionally, in the animal model of experimental allergic encephalomyelitis TBI has been shown to be associated with neurological deterioration [7]. Despite these limitations combination TBI and chemotherapy, such as cyclophosphamide and anti-thymocyte globulin, are regularly endorsed. More consensus is emerging regarding cell source. As opposed to marrow, peripheral stem cells mobilized by cyclophosphamide followed by granulocyte colony stimulating factor engraft more quickly and lack the requirement of general anesthetic for harvesting.

BMT is a therapy with undetermined efficacy but has considerable potential to benefit some MS patients at what may for some be an acceptable risk. Resolving questions of safety, efficacy and methodology will require a systematic and careful approach. The modest information derived from these four patients support the momentum to proceed with such efforts.

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