

Autologous Stem Cell Transplants in Treatment of Multiple Sclerosis: Where We Stand and Future Prospects

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Abstract

Based on experimental and clinical observations, high-dose immunosuppression followed by autologous transplantation may induce remissions in severe, refractory, autoimmune disorders including multiple sclerosis, a disease which, in its progressive form, does not respond to treatment. Phase I/II studies of transplantation in MS published by individual centers as well as a comprehensive analysis of the reports to the EBMT registry have shown that transplantation may positively affect MS by stabilizing the clinical condition of the patients, by improving their disability status, and by completely abrogating the inflammatory process in the brain as evidenced in magnetic resonance imaging. Other available therapies do not appear to be so efficacious as transplantation. However, the procedure is associated with a transplant-related mortality risk of about 3 to 8%. Therefore, it cannot be recommended for the treatment of a chronic, non-lethal, disease like MS unless it proves superior to standard therapies in terms of efficacy. This can be demonstrated only in a randomized trial, which is being launched by the EBMT under the name ASTIMS. It compares the BEAM regimen plus autotransplantation to mitoxantrone, which is currently regarded as one of the best available treatments, in patients with secondary progressive or rapidly evolving relapsing/remitting multiple sclerosis.

Intensive myelo/immunosuppressive therapy followed by bone marrow or peripheral blood hematopoietic stem cell transplantation (SCT) has recently been proposed for the treatment of severe, active, and refractory to standard therapies autoimmune diseases (AD) including multiple sclerosis (MS). The concept is based on data from animals showing remissions of autoimmunity after experimental transplantation as well as on clinical observations in patients with AD undergoing allogeneic (allo-) or autologous (auto-) SCT for concurrent malignancies [1-5].

MS is a common, crippling, organ-specific, T cell-mediated autoimmune disease directed against CNS myelin components. The pathological hallmark of MS is the demyelinated plaque which results from local inflammation and leads to focal neurological dysfunction. Clinically, MS runs initially a relapsing/remitting course (RR-MS; 80% of cases) followed after 5 to 15 years, in most patients, by a secondary progressive course (SP-MS) with or without superimposed disease exacerbations

(relapses). In 10-20% of cases, MS has a primary chronic progressive course (PP-MS) from onset, notorious for its refractoriness to therapy. Life-expectancy of MS patients is reduced by about 10 years while in a small percentage of patients survival is extremely short despite treatment ("malignant" MS). Steroids, cytotoxic drugs, and immunomodulators, like interferon- β (IFN- β) and copaxone, have been shown to reduce disease activity and probably progression, but the results are unpredictably variable. For the rapidly evolving RR-MS as well as the chronic progressive forms (SP-MS, PP-MS) there is still no widely accepted and meaningfully active therapy. There are patients, therefore, in whom alternative therapies could be investigated, such as high-dose immunosuppression with stem cell rescue (SCT). Good results of SCT in an animal model of MS (experimental allergic encephalomyelitis) using alloSCT or autoSCT have substantiated this concept provided that intensive chemotherapy is given, along with ex-vivo lymphocyte purging (in the autologous setting) [2,6].

Moreover, clinical observations of occasional patients with MS who improved after transplantation for malignancy seem, too, to support the concept [7,8].

Based on this evidence, we initiated in April 1995 a study of autoSCT in MS and the results were published on two occasions [9,10]. Since then, we have treated 35 clinically deteriorating patients who had failed standard therapies. The majority suffered from SP-MS (57%), 40% had PP-MS and one patient had rapidly evolving RR-MS. Median time from diagnosis was 7 years (range, 1-16). The patients had a high median extended disability status scale (EDSS) score of 6 (range, 4.5-8) and in 34% of them activity of the disease was also evident in magnetic resonance imaging (MRI) scans, judged by the presence of gadolinium-enhancing, or new, or enlarging, lesions in the brain. Twenty-five patients received the BEAM regimen (BCNU/etoposide/cytarabine/melphalan), and 10 received high-dose busulfan (16 mg/kg over 4 days) for conditioning. Antithymocyte globulin (ATG) was also administered after the infusion of the peripheral blood stem cell graft, for in-vivo T cell depletion. Blood stem cells were mobilized with cyclophosphamide (CY) at 4 g/m² plus G-CSF. Ten of 15 patients who received BEAM also received CD34+ cell-selected grafts. Medical, grade 3 or 4, manageable, toxicities occurred in most patients, particularly in those who had received ex-vivo manipulated grafts. One patient died from an invasive fungal infection (transplant-related mortality, TRM, 3%). A degree of neurological decompensation developed, as well, in 37% of the patients during the early post-transplant period, probably owing to fever, infection, or the use of G-CSF, but it was transient. At a median follow-up period of 35 months (range, 3-67), and despite a prolonged CD4+ cytopenia, no serious late effect had occurred (myelodysplasia or leukemia), except for a case of autoimmune thyroiditis, as has also been observed after treatment of MS with Campath-1H or IFN- β . In terms of efficacy, striking clinical improvements were observed in 15 patients (53%) [9] and the probability of confirmed-progression-free survival (cPFS) at 3 years post transplant was higher than with any other treatment, being 90% for SP-MS and 65% for PP-MS patients. MRI activity was significantly reduced post transplant [10].

Other studies have yielded similar results [11-15]. Kozak and Havrdova have published on 11 cases with SP-MS treated with BEAM with or without ATG, depending on ex-vivo T cell-depletion. The results have been updated recently on a total of 15 patients. Infections were the major toxicity but there were no toxic deaths or untoward late effects. Fourteen patients (93%) were stable or improved at a median follow-up of 20 months (range, 4-38) [12,16]. Mancardi and Saccardi have investigated the effect of autoSCT on MRI enhancing activity [15,17] in a co-operative, multi-center, phase II study of rapidly evolving SP-MS. Complete suppression of all gadolinium-enhancing lesions in all 18 patients was detected, an effect which has never before been observed with any other treatment and was sustained with time (median follow-up, 21 months; range,

2-42). Similar results have been reported by Saiz and Carreras [14]. However, oligoclonal IgG bands can still be found in the CSF and brain atrophy does not seem to halt in the early post-transplant period. This means that although the inflammatory process can be completely repressed by autoSCT, axonal degeneration can still go on, and indicates that autoSCT should be performed early in the course of the disease, before degeneration starts.

The registry of the Autoimmune Disease Working Party of the European Group for Blood and Marrow Transplantation (EBMT) now contains 122 reports of MS patients treated with autoSCT in Europe, Asia, and Australia (a smaller number of cases have also been reported to the American registry). Using uniform criteria of response, we have analysed the first 85 cases of the EBMT registry. Median age was 39 years (range, 20-58). The patients were severely disabled, with a median EDSS score of 6.5 (range, 4.5-8.5). They were treated with regimens of high-intensity (busulfan or TBI based), intermediate intensity (BEAM), or relatively light intensity (CY-based), along with ATG in 78% of the cases. Most of them (93%) received blood stem cell grafts, either unmanipulated or purged (61%). Five toxic deaths were reported (TRM, 6%), owing to infection (four) and heart failure (one). Two more patients died of progressive disease. At a median follow-up time of 16 months (range, 3-59), confirmed progression of disability was detected in 10 patients, while 59 were in stable (47 cases) or improved (12 cases) neurological condition. The probability of cPFS at 3 years was 72% (the deceased included), and was higher (78%) for all disease types except PP-MS. Moreover, MRI activity was found markedly reduced after transplantation [18].

The results of all these published phase I-II studies indicate that autoSCT is feasible in MS and has a possible clinical benefit, especially in SP-MS and young patients. Its most striking effect is on MRI, showing complete abrogation of the inflammation in the majority of cases. However, there is a TRM risk ranging from 0 to 8%, especially for the elderly, for those with high EDSS scores, and possibly for those receiving ex-vivo purged grafts. It is most probable that, with selection of patients having a high chance of response, the mortality risk can be brought down to less than 5%. It seems, therefore, proper to pursue studies of autoSCT in MS in order to clarify its therapeutic role. However, it is difficult to accept results of open phase I-II trials with unblinded assessments of neurological status in a disease in which it is notoriously difficult to judge the effect of a therapy. Thus, the only proper way to demonstrate the efficacy of autoSCT in MS is to show it in a multi-center, randomized trial. Such a comparative study is going to be launched by the EBMT under the title ASTIMS, i.e. Autologous Stem Cell Transplantation International Multiple Sclerosis Trial. Patients under 50 with rapidly evolving RR-MS or SP-MS and no medical contraindications or mental dysfunction precluding SCT will be randomized to receive either the BEAM regimen plus ATG or the "so-called" best, currently available,

treatment of progressive MS, i.e. mitoxantrone. Patients on the autoSCT arm will be rescued with peripheral blood stem cells mobilized with CY at 4 g/m² plus G-CSF. There will be no ex-vivo lymphocyte purging in this study, as no benefit of this procedure has been seen so far in humans. The protocol is being finalized and patient enrollment is scheduled to start in early Fall 2002. It is estimated that about 200 patients are needed to enroll in the study which will take five years to be complete. Then, we shall hopefully know whether autoSCT has a place in the management of MS or if we should discard it in order to spare the patients a potentially dangerous and costly therapy.

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