ADVANCES IN MULTIPLE SCLEROSIS TREATMENT: LONG-TERM OUTCOMES OF AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system (CNS) caused by autoimmune reactivity of T cells towards CNS myelin components. Conventional therapies do not provide satisfactory control of MS due to their inability to eradicate self-specific T cell clones. Recently, high-dose immunosuppressive therapy (HDIT) with autologous hematopoietic stem cell transplantation (auto-HSCT) was proposed as a new and promising therapy for MS patients. The rationale is that ablation of an aberrant immune system followed by reconstitution of a new immune system from hematopoietic stem cells may alter the characteristics of the T-cell responses and other immunological properties which may improve the clinical course of MS.

Since 1995, several clinical studies have addressed the issue of feasibility and efficacy of HDIT+auto-HSCT in MS and a certain clinical benefit was shown. Therefore, information about long-term outcomes of HDIT+auto-HSCT is of much importance. In addition, the patient selection criteria for HDIT+auto-HSCT are still unclear and the proper selection of patients for transplantation remains a key issue. We proposed 3 strategies of HDIT+auto-HSCT. Early HSCT (in MS patients with EDSS 1.5-3.0) is performed soon after diagnosis in case of primary refractory disease or poor prognosis. Conventional HSCT (EDSS 3.5-6.5) is performed in patients with secondary refractory disease. Salvage HSCT (EDSS 7.0-8.0) is an option in case of high disease activity and rapid neurological deterioration in late stages of the disease.

Of much importance are the results of a prospective Phase II multicenter trial initiated in 1999 by the Russian Cooperative Group for Cellular Therapy. By now 109 patients with various types of MS (secondary progressive – 51 patients, primary progressive –19, progressive-relapsing – 8, and relapsing-remitting – 31) from 6 medical centers are included in this study (mean age - 33.0, range: 17-54; male/female – 49/60). Seventy patients underwent conventional HDIT+auto-HSCT; 32 patients – early HDIT+auto-HSCT and 7 patients – salvage HDIT+auto-HSCT. BEAM or BEAM modified conditioning regimens were used. Clinical and patient-reported outcomes were analyzed. Median EDSS at base-line was 5.0 (range 1.5 – 8.0). The mean follow-up duration was 18 months (range 6 – 90 months). All of the patients had previously undergone conventional treatment. Neurological and QoL evaluation was provided at baseline, at discharge, 3, 6, 9, 12 months, and then every 6 months after HDCT+ ASCT. MRI was conducted at baseline, at 6, 12 months, and at the end of follow-up.

Notably, no transplant-related deaths were registered. Transplantation procedure was well tolerated by the patients. The efficacy analysis was performed in 79 patients. At 6 months post transplant the following distribution of patients according to clinical response was observed: 42 patients (53%) achieved an objective improvement of neurological symptoms (defined as a $\geq$0.5 point decrease in the Expanded Disability Status Scale EDSS score as compared to the baseline and confirmed over 3 months), and 37 patients (47%) had disease stabilization (steady EDSS level as compared to the baseline and confirmed over 3 months). Among the patients with improvement there were 25 patients after conventional HDIT+auto-HSCT, 15 - after early HDCT +auto-HSCT and 2 - after salvage HDCT +auto-HSCT. Among the patients with stabilization there were 23 patients after conventional HDCT +auto-HSCT, 9 - after early HDCT +auto-HSCT and 5 – after salvage HDCT +auto-HSCT. At long-term follow-up clinical response in 40 patients (50.6%) was classified as improvement; 34 patients (43.1%) remained stable. Two patients deteriorated to a worse score after 18 months of stabilization (SPMS and PPMS; conventional auto-HSCT), one patient – after 6 months of stabilization (SPMS, conventional auto-HSCT); 2 others progressed after 12 and 30 months of improvement (SPMM, conventional auto-HSCT and RRMS, early auto-HSCT, respectively). No active, new or enlarging lesions were registered in patients without disease progression.
Out of 41 patients included in QoL analysis 39 exhibited improved QoL 6 months post-transplantation. Further QoL improvement was observed at longer follow-up. Thus, QoL response was achieved in 39 out of 41 patients.
All the patients without disease progression were off therapy throughout the post-transplant period.
Of special interest is the group of patients which underwent early transplantation (mean age - 28 years, median EDSS - 2.0). All 23 patients included in the analysis responded to the treatment –15 patients experienced improvement; 8 patients – stabilization. One patient in the group (male, 25 y.o.) relapsed 2.5 years after transplantation. Remarkably, one patient (female, 31 y.o.) experienced a significant decrease in EDSS from 3.0 at base-line to 1.5 at 3 months post-transplant. At 18 months after transplantation a further decrease in EDSS by 0.5 took place.

In conclusion, this study provides ample evidence in support of HDIT+ auto-HSCT and its efficacy in the treatment of MS patients. At long-term follow-up the vast majority of patients exhibited clinical response categorized as either improvement or stabilization. QoL response was also observed in these patients. The results obtained show that transplantation appears to be effective in patients with various types of MS. Identification of treatment strategies based on the level of disability, namely early, conventional or salvage transplantation, appears to improve treatment outcomes. Our data support the idea that HDIT+auto-HSCT is more effective in young patients with early stages of rapidly progressing disease.

The rationale of evolution from myeloablative to non-myeloablative transplant regimens should be confirmed by further studies. Their goal should be to establish the best timing for transplantation and to validate HDIT+auto-HSCT regimens in patients receiving early, conventional or salvage transplantation.