BONE MARROW STEM CELL TRANSPLANTATION IN MULTIPLE SCLEROSIS

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Bone marrow or Hematopoietic stem cell transplantation (BMT, HSCT), both allogeneic and autologous, has become one of the hottest areas of clinical immunology. One of the main autoimmune diseases, in which HSCT was extensively tried during the last decade, is Multiple Sclerosis (MS). Autologous HSCT (ASCT) relies on an extensive debulking of the autoaggressive immune system, followed by the re-infusion of the patients' HSC (commonly identified as CD34+ cells). The allogeneic procedure is based on the substitution of the faulty immune system by a new healthy one, theoretically capable of eradicating the autoimmune clones by means of the classical combination of high-dose immunosuppressive therapy and a Graft versus- Autoimmunity (GVA) effect.

Experimental data from our group in the animal models of MS (EAE), showing that BMT can suppress EAE and induce long-lasting tolerance, have provided the scientific basis for such therapeutic approach. Few clinical papers and many anecdotal reports have indicated a beneficial effect of this treatment in MS, leading in stabilization or improvement in a great proportion of the treated patients.

More than 400 patients have so far been treated worldwide. Since 2000, all communications have invariably reported a dramatic, almost 100%, reduction in, or disappearance of the inflammatory activity of MS, on magnetic resonance imaging (MRI) which is retained with time. Also, brain atrophy which seems to continue after HSCT as a result of oedema resolution slows down after the 2nd post-HSCT year. Patients with severe inflammation in the CNS experience substantial improvements of their disability status. The most impressive clinical effect has been recently demonstrated in a study which included patients with low disability and a non-myeloablative conditioning protocol. On the other hand, patients with long-standing disease and those with primary progressive MS, i.e. cases in which the neurodegenerative component of the disease prevails, may not respond to HSCT. This has been detected clinically and also in histopathological examinations of autopsy material, which showed ongoing demyelination and axonal damage despite marked suppression of inflammation.

With regard to clinical results of HSCT, it must first be noted that the great majority of the patient series treated worldwide had advanced disease with median
EDSS scores of 6 to 6.5 while about 20% of the patients had primary progressive MS. After HSCT, improvement of disability scores by 1 to 4 steps was observed with
a great reduction in the yearly relapse rate and a probability of disease progression-free survival (PFS) of 60-80% at three years. At 10 years post HSCT, PFS was around 65% for secondary and 40% for primary progressive MS. However, although, hundreds of MS patients have been treated with HSCT, different conditioning and treatment protocols have been used in each Center, making difficult to organize and summarize the results from all these small studies. Unfortunately, still, there is no completed controlled study with HSCT in MS.

The utilization of haemmatopoietic stem cells to suppress autoimmune cellular and humoral aggression must be distinguished from the use of stem cells to induce/promote neuronal regeneration, but both areas are tightly connected, as highlighted in the case of Mesenchymal stromal cells (MSC) which are also part of the bone marrow stem cell repertoire. The main role of MSCs is to support hematopoiesis but they can also give rise to cells of the mesodermal layers. MSC were shown to possess immunomodulatory effects and additional stem cells features, such as the self-renewal potential and multipotency. Their debatable transdifferentiation potential to cells of the endo- and exo-dermal layer, including cells of the CNS, may explain in part their reported neuroprotective effects. Studies in vitro and in vivo have indicated neuroprotective effects. MSCs are believed to promote functional recovery following CNS injury or inflammation, by producing trophic factors that may facilitate the mobilization of endogenous neural stem cells and promote the regeneration or the survival of the affected neurons. These immunomodulatory and neuroprotective features which were proven in EAE and various animals models indicate that MSCs may be potential candidates for the management of MS. A preliminary pilot clinical trial from our MS Center at Hadassah supports the clinical safety of this modality and a possible therapeutic role in MS.