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Intense immunosuppression and autologous hematopoietic stem cell transplantation for multiple sclerosis

In this issue of Haematologica, Carreras et al.1 of the Hospital Clinic, Barcelona, Spain, report the results of a phase I-II study of high-dose immunosuppressive chemotherapy followed by infusion of autologous peripheral blood, CD34+ cell-selected, hematopoietic stem cells for the treatment of patients suffering from rapidly progressing multiple sclerosis (MS). This novel therapy, i.e. immunosuppression to the point of immune ablation and autologous stem cell transplantation (ASCT), was introduced for the management of autoimmune diseases (AD) about ten years ago and, although still not generally accepted, has been used in a considerable number of centers worldwide to treat patients with severe disease, not responding to conventional therapies.2 MS is such an example, especially in its progressive forms. MS is a relatively common (~2 cases per 1000 population), incurable, crippling disease caused by a T-cell-mediated autoimmune process against myelin in the central nervous system (CNS) with subsequent axon loss and gliosis. By 15 years from onset, half the patients have lost the ability to walk unaided. The main aim of the treatment is to prevent disability, that is to halt disease progression. Unfortunately, the two existing treatment modalities, i.e. immunosuppression with conventional-dose cytotoxic drugs and immunomodulation with interferon-α or copaxone, fail to control progressive disease. Mitoxantrone has recently been claimed to have meaningful effects, but the duration of this therapy is limited because of its cardiotoxicity.

ASCT for MS was proposed in 1997.4 The study was based on the good results of syngeneic or pseud-autologous transplantation in the control of experimental autoimmune encephalomyelitis (EAE), an animal model of MS.5,6 High remission rates were attained when high-dose conditioning regimens were employed, while relapses depended on residual autoreactive cells surviving the conditioning, as well as on T-cells re-infused with the graft. How exactly ASCT can influence the course of EAE or MS is not fully resolved. There is an immediate beneficial anti-inflammatory effect in the CNS, due to the deletion of autoreactive clones, which can be easily attested by magnetic resonance imaging (MRI) and, possibly, by clinical improvement. ASCT has been shown to invariably suppress inflammation in the CNS to a degree which is not achieved by any other immunosuppressive therapy.7 This is in accordance with the well-known profound, and prolonged, immunosuppression observed after ASCT for malignant disease. Other therapies may also suppress inflammation in the CNS significantly, e.g. high-dose cyclophosphamide or the Campath-1H monoclonal antibody, but their effect is not durable. In addition, it seems that ASCT exerts not only immunosuppressive but also immunomodulatory activity. This has been demonstrated in cases of AD resistant to standard therapies, which became sensitive or could be managed with much lower drug-doses after transplantation. Tipping the immune balance towards suppressor mechanisms might explain this effect. A durable effect could also be expected from the possibility that ASCT could time-shift the autoimmune disease to an earlier, latent, phase and allow the immune system to develop from lymphoid progenitors by a process resembling normal ontogeny. There is still no proof, however, that transplantation can induce tolerance in this way. Another possible benefit is related to the capacity of stem cells to enter the CNS and transdifferentiate into microglia and neurons.8 In this way they could contribute to remyelination and neuronal repair, but this benefit is currently hypothetical.

Small scale phase I-II studies of ASCT for MS have been conducted since 1995. About 200 patients have been treated so far and more than two thirds of these have been reported to the Autoimmune Disease Working Party registry (ADWP) of the European Group for Blood and Marrow Transplantation (EBMT), which has published a comprehensive analysis of clinical outcomes in 85 rapidly progressing cases.9 The study showed the feasibility of the method, but also an associated mortality risk of about 6%, probably because of the inclusion of poor-risk patients. In terms of clinical efficacy, progression-free survival at three years was 74%, being higher for secondary progressive MS (78%) and for younger patients (89%). These probability rates are much higher than those achieved with any other, or placebo, therapy but, given the well-known difficulties in assessing MS patients neurologically, the clinical benefit of ASCT remains to be validated only in controlled trials. Individual centers participating in the

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EBMT study have further updated their data in separate reports analyzing their results in view, also, of newer developments in the understanding of the pathogenesis of MS. It has only recently been stressed that accumulation of disability does not solely depend on inflammation but also on axonal degeneration which may occur either as a result of inflammation-demyelination or even early in the course of the disease due to unclear causes which may or may not be immune-mediated. Consequently, disability might continue to progress in the absence of inflammation. This is a disturbing argument against immunosuppressive therapies, including ASCT. In fact, the group at the Hospital Clinic, Barcelona, was one of the first to report that MRI-detected brain atrophy, which reflects axonal degeneration, may continue after transplant, even if there is no evidence of inflammation, a finding confirmed by other groups, too. This shrinking of the brain was mainly observed in the early post-transplant period and it is unknown whether it is due to axon loss or to abrogation of the inflammatory edema. If the latter is true, one could expect this brain atrophy to slow down over time.

It must be stressed that ASCT is still an investigational treatment for MS. It seems to have the best anti-inflammatory effect, as shown by MRI scans, but its clinical value is yet to be demonstrated in a phase III, prospective, controlled trial comparing ASCT with the best available treatment, namely mitoxantrone. Such a trial is about to be launched by the ADWP of the EBMT in order to resolve the issue of clinical efficacy, and centers are urged to participate in it, as very little can be expected from further phase I–II trials. It should also be remembered that patient selection is of crucial importance; not only because of the mortality risk, especially if very strong conditioning regimens or extensive T-cell depletion are applied, but also because intensive immunosuppression will be useless in types of MS characterized by neurodegenerative rather than inflammatory lesions, for example, in patients with primary progressive MS, those with long-standing disease, and those with high disability (EDSS) scores. Good candidates for ASCT are young patients with rapidly evolving relapsing–remitting MS, patients with the so-called malignant form, and those with secondary progressive MS having EDSS scores below 6.5, inflammation in the CNS, and clinical deterioration of at least one EDSS point in the last year. Treating such patients offers a high chance of response at a minimal mortality risk.

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References


Chronic graft-versus-host disease after allogeneic peripheral blood transplantation

In this issue of the Journal, Mengarelli et al. report a lower incidence of chronic graft-versus-host disease (GVHD) after allogeneic transplantation of granulocyte colony-stimulating factor mobilized peripheral blood stem cells (allo–PBT) by prolonging cyclosporine A (CsA) administration over 12 months. Allo–PBT, instead of allogeneic bone marrow transplantation (allo–BMT), is associated with earlier hematopoietic and immunologic recovery, without a significant increase in acute GVHD. However, some series of allo–PB have reported a higher incidence of chronic GVHD. This observation is restricting the wider use of peripheral blood as a source of stem cells for allogeneic transplantation. There is no doubt that chronic GVHD is a major cause of morbidity and