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,[10] 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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Chronic graft-versus-host disease after allogeneic peripheral blood transplantation

In this issue of the Journal, Mengarelli *et al.*[1] 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.[1] However, some series of allo-PBT have reported a higher incidence of chronic GVHD.[3-5] 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

mortality, accounting for about 25%-33% of deaths in long-term survivors of transplants, and that it is the main cause of delay in recovering an adequate quality of life after the transplant.[6] The most important complication associated with chronic GVHD is immunodeficiency, leading to susceptibility to opportunistic infections and second neoplasms.[7] On the other hand, chronic GVHD has been associated with a potent antileukemic effect. Thus, patients developing this complication have a lower incidence of relapse after transplantation.[8] The final clinical result, taking into account these detrimental and beneficial effects, of chronic GVHD has been analysed in patients submitted to allo-BMT. It seems that for those patients who receive a transplant in an advanced phase of disease, chronic GVHD might be associated with a better survival rate.[9] In contrast, for patients at low risk of relapse the potential benefit of the antileukemic effect is counterbalanced by its mortality, with the final result of an adverse impact on survival in this group of patients.[10] Unfortunately, the clinical effect of chronic GVHD depending on its severity (e.g. limited vs extensive) is not specified in these articles. Has chronic GVHD the same clinical consequences after allo-PBT as after allo-BMT? Extensive chronic GVHD after allo-PBT has been associated with high transplant-related mortality.[5,11] However, it is of note that the association of chronic GVHD with reduced relapse rate reported in the allo-BMT setting has not been found in some of the most important series of allo-PBT.[2-4] Two recent reports have shown that extensive chronic GVHD after allo-PBT adversely affected the outcome.[5,11] Although the clinical impact on the outcome of chronic GVHD after allo-PBT requires continued long-term evaluation and a better definition of the effects of limited and extensive chronic GVHD in patients with early or advanced phases of disease, it seems prudent to incorporate methods to decrease the incidence of this complication after allo-PBT. T-cell depletion of the graft is the only known method of GVHD prophylaxis consistently associated with a reduction in chronic GVHD after allogeneic transplants. However, this approach is associated with a higher relapse rate, which limits its use to patients with a low probability of relapse. Another alternative is to employ an *in vivo* modulation of T-cells post-transplant, by prolonging CsA administration. In this issue Mengarelli *et al.*[1] show for the first time in the setting of allo-PBT that this approach reduces the incidence of extensive chronic GVHD. Although overall survival was not modified, we may assume that patients benefited from an improved quality of life.

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Advances in unrelated donor hematopoietic cell transplantation

For patients without an HLA-identical sibling, transplantation of hematopoietic stem cells from HLA-compatible unrelated volunteer donors has become feasible thanks to the expansion of registries of HLA-typed volunteers that now include more than seven million individuals worldwide. The probability of matching patients with at least one donor for HLA-A, B and DR has increased as a function of the logarithm of the donor pool. In the National Marrow Donor Program of the United States, such a probability was 50% with a pool of 100,000 donors and has expanded to 85% with a pool greater than two million donors typed for HLA-A, B and DR. Utilization of unrelated donors as a source of hematopoietic stem cells has also increased because of improved safety of trans-