FTY720 in hematopoietic cell transplantation

FTY720 no transplante de células hematopoéticas

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The potential therapy for hematological malignancies is allogeneic hematopoietic cell transplantation (HCT). It has been shown that stronger graft-versus-leukemia/lymphoma (GvL) effects occur in the presence of stronger graft-versus-host (GvH) alloreactivity associated with extensive MHC mismatches.[1-3] Acute degrees (II-IV) of graft-versus-host disease (GVHD) are observed in 25-60% of HLA-identical related-donor HCT and in 45-70% of matched unrelated transplant recipients[4-6] and this remains the major cause of morbidity and mortality in patients undergoing allogeneic bone marrow transplantation.[7,8] The usual immunosuppressive drugs such as cyclosporine A, prednisone, and methotrexate[9-11] have not successfully eliminated GvHD.

FTY720 is a synthetic compound based on the metabolite of ascomycete *Isaria sinclairii* which has shown GvHD-inhibitory activity when rat spleen cells were transplanted from a parental strain into F1 rats treated with 200 mg/kg cyclophosphamide[12] and in a rat small-bowel transplant model.[13] Kim *et al.*[14] showed that lethally irradiated mice reconstituted with allogeneic BMCs plus spleen cells and treated with FTY720 (3 mg/kg/day) presented a decrease in the mortality rate besides reduced clinical GvHD. The group also observed that GvL effects after the administration of leukemia/lymphoma T cell line were not impaired in mice receiving BMCs plus spleen and treated with FTY720.

These encouraging results suggest the possible use of FTY720 in hematopoietic cell transplantation. In order to

contribute to the better understanding of FTY720 mechanisms of action as a monotherapy or in association with tacrolimus, Lopes *et al.* show in this issue the results from the experimental model of skin transplantation. FTY720 alone (1 mg/kg/day) or in combination with tacrolimus (2 mg/kg/day) during 21 days was associated with improved skin allograft survival in incompatible mice. Spleen and blood lymphocytes presented reduced numbers in mice treated with FTY720 alone and FTY720 + tacrolimus. The CD4+T expression in splenocytes was also reduced. Activation markers such as MHC II and ICAM-1 were less expressed in splenocytes from mice treated with FTY720. Skin graft infiltration was similar in non-treated and treated groups. In this model, the association with tacrolimus caused no improvement in the results observed in mice treated only with FTY720 suggesting that the FTY720 + tacrolimus combination was not synergistic and, on considering the side effects of calcineurin inhibitors, should not be used. On the other hand, the same group[15] recently showed that in mice FTY720 + tacrolimus caused less nephrotoxicity than Tacrolimus alone. Therefore the combination may be considered in cases of established renal toxicity as FTY720 seems to protect from the side effects caused by tacrolimus. These findings have an important clinical significance as the conditioning regimen (irradiation, chemotherapy + cytotoxic drugs) and CNIs amongst others are causative factors of nephropathy after HCT.[16]

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