Immune monitoring and adoptive immunotherapy following allogeneic hematopoietic stem cell transplantation - ABSTRACT

Allogeneic hematopoietic stem cell transplantation (aloHSCT) is a specialized therapeutic method that is potentially curative for a number of hematological and non-hematological diseases. Despite continuous advances in transplant medicine, the prognosis of patients is still limited by a number of post-transplant complications, dominated by relapse and graft-versus-host disease (GvHD). These complications affect the survival of patients, but also reduce their quality of life. So, we are looking for new treatment modalities that would improve their prognosis. One of the promising procedures in the treatment of GVHD is the administration of cells with immunomodulatory potential (immunotherapy). In a number of European centers, including ours, mesenchymal stem cells (MSCs) are administered to patients after alloHSCT in the steroid-refractory GvHD (SR-GvHD) indication. Invariant NKT lymphocytes are a new cell population with a promising potential to suppress GvHD and at the same time they potentiate the graft-versus-leukemia (GvL) effect. The introduction of these cell populations into clinical practice must be preceded by a number of preclinical studies and continuous optimization of manufacturing and application procedures must take place even during clinical administration.

In our work, we focused on comparing the properties of drugs from MSCs, their immunomodulatory potential and comparing single and multi-donor products. MSCs from batches from different donors did not differ significantly in a number of parameters after processing, cryopreservation and recultivation while maintaining good manufacturing practice, however, we proved that MSCs from batches from different donors differ in their proliferative potential and growth rate. On the other hand, mixing MSCs from different donors (so-called "pooling") did not increase their immunomodulatory potential. The total number of cells does not affect the immunomodulatory properties of MSCs if the minimum production dose is achieved. For our future practice of MSC application in the treatment of SR-GvHD, it still seems advantageous to use MSC in the mode of 1 patient - 1 donor. We also compared MSCs with iNKT lymphocytes in terms of their in vitro immunomodulatory potential. In preclinical testing, we compared several batches of cultured and expanded iNKT and MSCs from different donors. We quantified the expression of the activation marker CD25 on non-specifically stimulated mononuclear cells after co-cultivation with MSC or iNKT. We have shown that both cell populations are able to modulate immune responses in vitro to a similar extent. Because the HLA match between donor and recipient must be respected when administering iNKT drugs, we searched a suitable source of iNKT cells. We monitored the dynamics of iNKT regeneration in the context of immune system repair after allogeneic hematopoietic stem cell transplantation and examined whether an ideal timepoint could be determined for the collection of autologous iNKTs in patients. Kinetics during immune system regeneration after aloSCT were not linear and iNKT levels did not increase in all patients. The dynamics of iNKT regeneration was highly variable and depended on a number of peritransplantation factors, so it is not possible to determine with certainty a reliable timepoint when we could detect iNKT in peripheral blood in all patients. For this reason, in the preparation of the production protocol, we will focus on the use of allogeneic HLA of identical iNKT donors. Our goal will not be to replace MSCs in the treatment of SR-GvHD with a new population of iNKT, but to identify patients who will benefit from the individual treatment modalities. We assume that individual cell populations will not compete with each other, but may, on the contrary, complement each other in specific situations and thus lead to better results in the treatment of post-transplant complications.