Abstract

Graft Versus Host Disease Response in Co-cultivation of Mesenchymal Stem Cell and CD34+ Hematopoietic Stem Cell of Major Thalassemia

Background. The main problem in the implementation of bone marrow transplantation (BMT) in patients with thalassemia major in the world today is graft versus host disease (GvHD). One of the causes is incompatibility of the donor's human leucocyte antigen (HLA) with recipient T lymphocytes. The gene that plays the most role in this GvHD reaction is the donor human leucocyte antigen (HLA), and the HLA which has immunosuppressive properties is the non-classical class 1b HLA-G. HLA-G is found on the surface of mesenchymal stem cell (MSC) membranes. MSC when activated with T lymphocytes, will secrete immunosuppression molecules, HLA-G and forkhead box protein 3 (Foxp3), and express interleukin-10 (IL-10), transforming growth factor ß (TGFß), prostaglandin E2 (PGE2), and indoleamine-2,3-dioxygenase (IDO). MSC will induce $CD34^+$ hematopoietic stem cells to keep dendritic cells (DC) in immature (iDC) state which will strengthen the inhibition against the proliferation of $CD4^+$ and $CD8^+$ T cells, thereby reducing the GvHD reaction.

Methods. The research design was carried out as an experimental pre-posttest only control group design (in-vitro). T lymphocytes cultured from peripheral blood of children with thalassemia major were exposed to MSC and $CD34^+$ hematopoietic stem cells from sibling donor. The experimental unit was divided into 4 groups: (1) The positive control group, untreated T lymphocytes, (2) T lymphocytes exposed to MSC, (3) T lymphocytes exposed to $CD34^+$ hematopoietic stem cells, (4) T lymphocytes exposed to co-cultivation of MSC-$CD34^+$. Elisa examination of IL-10, TGFß, PGE2, IDO secretion and immunocytochemistry examination of the expression of HLA-G, Foxp3, $CD4^+$, and $CD8^+$ were done at 0, 12, and 24 hours incubation time.

Results. Co-cultivation of MSC-$CD34^+$ stem cells in T lymphocyte culture was able to increase the secretion of IL-10, TGFß, PGE2, IDO, HLA-G and Foxp3 significantly ($p < 0.05$) at 12 and 24 hours. $CD34^+$ hematopoietic stem cells and MSC-$CD34^+$ stem cell co-cultivation were able to significantly reduce $CD4^+$ expression ($p < 0.05$) at 12 and 24 hours. Furthermore, MSC and MSC-$CD34^+$ stem cell co-cultivation were able to reduce $CD8^+$ expression significantly ($p < 0.05$) at 24 hours.

Conclusions. Co-cultivation of MSC-$CD34^+$ hematopoietic stem cells in T lymphocyte culture was able to reduce the GvHD reaction.

Keywords: BMT Thalassemia, MSC umbilical cord mesenchymal stem cells, $CD34^+$ hematopoietic stem cells, IL-10, TGFß, PGE2, IDO, HLA-G, Foxp3, $CD4^+$, $CD8^+$.

Promotor,

Prof. Dr. Fedik Abdul Rantam, drh., M.Sc