5. Gene Therapy (GT)

Principles

- To ensure patients and families receive adequate information on gene therapy for informed decision-making.
- To ensure close follow-up of patients who have undergone gene therapy.

Recommendation

- The discussions of Gene Therapy should be initiated by the specialist centre and, if the patient is serious about pursuing gene therapy and it is appropriate, referral should be made to a centre where experimental trial is opened.
- Before referring to a GT trial, search for a HLA matched donor should be done in order to state no matched donor is available.

Background

Gene therapy is a promising curative option for patients with thalassemia major. It is still in its beginning and is available only through experimental trials. No trials are currently opened in Canada, but several trials are ongoing or in late phase of development in the United States and Europe.

The hematopoietic stem cells (HSC) of the patient are collected in peripheral blood by apheresis after stimulation by GSCF and Plerixafor. Then, the normal gene of hemoglobin is introduced within autologous HSC in a dedicated laboratory for gene therapy. Several technologies can be used to transfer the gene into HSC[183]. Currently, the most common technology is based on a viral vector called lentivirus[184]. This virus does not cause infectious disease. Once the corrected HSC are produced, the bone marrow of the patient has to be destroyed by high doses of chemotherapy, similar to conditioning regimen of autologous HSCT, before infusing the corrected HSC intravenously.

Current GT trials enroll only patients who lack a HLA matched donor. Since 2004, more than 25 patients have been treated by GT[184,185]. In the largest reported trial, 18 patients from 12 to 35 years of age were included. All patients without the β0/β0 form of thalassemia became transfusion independent, while the 8 patients with β0/β0 thalassemia remained transfusion dependant but at lower rate[186]. In another trial based on the same vector, 4 patients, all without β0/β0 thalassemia, achieved transfusion independence[187].

The main risk associated with GT is secondary leukemia related to dysregulation of normal genes by the random insertion of the viral vector into the genome of HSC. So far, it has not been observed in GT for thalassemia but the length of follow-up is still too short to conclude. GT induced leukemia have been observed only in several GT trials based on a retrovirus vector, different from the lentivirus vector used in GT for thalassemia, for treatment of various immune deficiencies[188-190]. Also, patients enrolled in GT trials are at risk of secondary loss of the corrected HSC due to clonal exhaustion[183]. Moreover, patients are exposed to long term sexual hormone insufficiency and hypofertility related to high doses of chemotherapy. Patients have to be informed that GT brings a corrected hemoglobin gene to HSC only, but not to egg cells and spermatozoids which will always carry the mutated gene.

Finally, there has been recent advent of the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated protein 9 (Cas9) systems for precise genome editing. Inherited haematological disorders represent ideal targets for CRISPR-Cas9-mediated gene therapy. Correcting disease-causing mutations could alleviate disease-related symptoms in the near future. Similar to virus-mediated gene therapy, CRISPR-Cas9-mediated genome editing is used to correct HBB gene mutations in patients via HDR, leading to normal erythropoiesis. In the past two years, several research groups have successively applied CRISPR-Cas9 technology to correct β-thalassaemia mutations in patient-derived induced pluripotent stem cells (iPSCs).[476]

Interventions

- Discussions about gene therapy for thalassemia should include benefits, risks, short and long-term complications, quality of life and psychosocial impact.
- The patient's risk factors and organ function should be assessed prior to GT.
- Possible short and long-term complications of gene therapy include secondary leukemia or lymphoma, secondary loss of corrected HSC, delayed pubertal development, endocrine deficiencies, and infertility.
- Preservation of fertility should be part of the preparation to gene therapy. For prepubertal children, enrolment in investigational trial of tissue preservation (either ovarian or testicular tissue) should be considered.
- Transplanted individuals should be counseled that they will still pass on a mutant thalassemia gene to each of their children.