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SEED HAEMATOLOGY

Haematopoietic stem cell transplantation – part 1

This SEED informs about the stem cells, their aetiology and sources as well as general facts about haematopoietic stem cell transplantation (HSCT).

Haematopoietic stem cells

Haematopoietic stem cells reside in the bone marrow, primarily of the pelvis, femur and sternum, at an estimated frequency of one per 10 000 haematopoietic cells. At an even lower frequency (1 per 100 000) they can also be present in peripheral blood. The two most important properties that define a stem cell are self-renewal and pluripotency. Self-renewal means that a stem cell can divide asymmetrically to produce a progenitor cell with limited self-renewal potential and another true stem cell, thus sustaining a haematopoietic stem cell pool over the whole lifetime of an individual. Pluripotency means that one cell has a potential to differentiate into any type of blood cell – a white blood cell, red blood cell or platelet.

Morphologically, stem cells are indistinguishable from other undifferentiated precursor cells or leukaemic blasts. They express a surface glycoprotein, CD34, which disappears as the cell undergoes differentiation. For this reason, CD34 is used as a marker for haematopoietic stem cells.

Haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation (HSCT) is a treatment that involves the elimination of a patient's haematopoietic system by chemotherapy or radiotherapy and replacing it either with stem cells previously harvested from this patient or with cells from another individual (donor). HSCT allows the use of a more vigorous therapy in patients with resistant tumours. Apart from that, the transplanted cells themselves may have a curative effect on the haematological malignancies of the patient.

There are three types of HSCT: **autologous**, allogeneic and syngeneic. In autologous transplantation, haematopoietic stem cells are collected from the patient prior to a course of aggressive anti-cancer treatment (either chemotherapy or radiotherapy), which will destroy the bone marrow, and re-infused afterwards. In **allogeneic** transplantation, stem cells are collected from another individual, who can be either related or unrelated to the patient. In **syngeneic** transplantation, haematopoietic stem cells collected from an identical twin are used.

Prior to transplantation, recipients undergo a procedure called 'conditioning': chemotherapy eradicates tumour cells

as well as haematopoietic and immune cells, preparing the bone marrow for engraftment of transplanted stem cells. Infused stem cells migrate to the haematopoietic niche in the bone marrow due to chemotaxis – a process called 'homing'. Over time, engrafted stem cells differentiate to reconstitute the destroyed haematopoietic system of the host.

In autologous transplantation, patients undergo chemotherapy twice: before stem cell collection and after that. The second chemotherapy is then followed by the transplantation. During the first course of therapy, usually a weaker one, most of the tumour cells are destroyed and stem cell proliferation in the bone marrow is stimulated. The second course of therapy aims at destroying the remaining cells – malignant and non-malignant – in the bone marrow to prepare the marrow for the engraftment of transplanted stem cells.

The broad spectrum of disorders where HSCT is indicated includes malignant diseases such as leukaemia, lymphoma, multiple myeloma, myeloproliferative neoplasm and solid tumour, and also non-malignant diseases like thalassaemia, aplastic anaemia and many other inherited and acquired diseases of the haematopoietic system (Fig. 1).

With adults, significantly more autologous transplantations are performed than allogeneic ones; the most common indication for autologous transplantation is multiple myeloma, whereas for allogeneic transplantation it is acute myeloid leukaemia. With paediatric patients, allogeneic transplantation is more frequently used than autologous transplantation. Most allogeneic transplantations performed in children are cases of acute leukaemia and non-malignant indications, such as primary immunodeficiency and haemoglobinopathy. Autologous transplantations in children are mostly performed for the treatment of lymphomas and solid tumours.

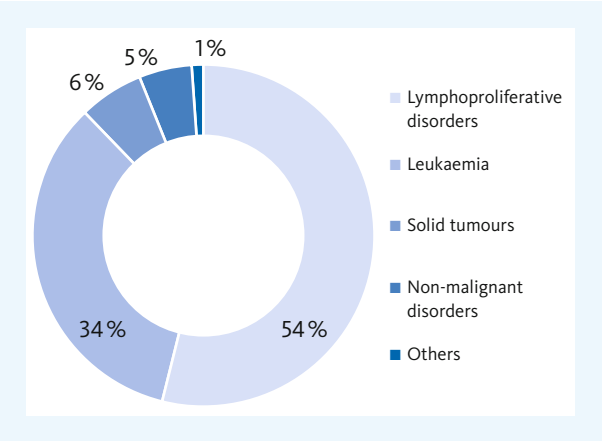

Fig. 1 *Main indications for HSCT with adults*

Sources of haematopoietic stem cells

Currently three sources of stem cells for HSCT are used: bone marrow, mobilised peripheral blood, and umbilical cord blood.

The classic source of stem cells for transplantation is **bone marrow**. Around 3% of the cells in bone marrow express the stem cell marker CD34. Bone marrow is harvested from the pelvic bone under general or local anaesthesia. European guidelines limit bone marrow removal to 15 mL/kg of donor body weight. The marrow is then filtered to remove clots and fat. In case of mismatched ABO blood groups between the donor and recipient in allogeneic bone marrow transplantation, red blood cells may also be eliminated. In autologous bone marrow transplantation, a procedure called 'purging' can be performed in order to remove possible tumour cells from the aspirated bone marrow. Marrow can be cryopreserved and used later or directly infused into the recipient.

Nowadays – for transplantation purposes – bone marrow stem cells have almost fully been replaced by peripheral blood stem cells, which offer a number of advantages. Compared to bone marrow, **peripheral blood** stem cells are easier to harvest: the procedure is less invasive, less painful and requires no anaesthesia. Compared to bone marrow donation, twice as many stem cells can be harvested from one donor after a mobilisation procedure; another advantage is that peripheral blood stem cells engraft faster, which means that the recipient will recover several days earlier.

Foetal blood is relatively rich in immature cells. Stem cells can therefore be harvested from **umbilical cord blood** drained from a placenta after birth. 40 – 100 mL of cord blood can be obtained from one placenta. The procedure is non-invasive and simple. A large advantage of cord blood is the immature state of the immune cells, which means that less stringent genetic compatibility is required. Cord blood transplants are used when no matching donor can be identified. However, the concentration of stem cells in cord blood is lower than in bone marrow and mobilised peripheral blood, which means a lower number of stem cells are available for transplantation, and therefore a longer recovery time of haematopoiesis would be expected, which is associated with a higher risk of infection in the post-transplantation period. Due to the lower number of harvested stem cells, cord blood transplantation is usually used in paediatrics. The reason is that children, due to their lower body weight, require in total a lower number of stem cells to be infused.

Immunology of HSCT

Chemotherapy, which is used to treat cancers, acts primarily on proliferating cells. Cancer stem cells, just like normal stem cells, are quiescent, which means that they divide very rarely and are therefore insensitive to this type of therapy. It is very difficult to eradicate all cancer stem cells, which is the main reason for relapse.

Stem cell transplantation allows the use of higher doses of chemotherapy or radiation, which otherwise would be fatal due to permanent bone marrow failure as an effect of the therapy. However, a certain rate of relapse is noted for autologous and syngeneic transplantations, because dormant cancer stem cells either evade the cytotoxic effect of the therapy or are re-introduced to the body with the transplant.

After the discovery and typing of human leukocyte antigen (HLA) genes, it became possible to perform allogeneic HSCT, which further improved therapy outcomes. Compared to autologous transplantation with its main purpose of reconstituting haematopoiesis after chemo- or radiotherapy, allogeneic transplantation additionally offers a curative effect due to immunological interactions between the donor and host cells.

HLA genes encode major histocompatibility complex (MHC) surface proteins that play a role in the immune system by presenting antigens to T-cells. MHC class I molecules are expressed on all nucleated cells in the body and generally present endogenous peptides to CD8+ cytotoxic T-cells, contributing to the mechanism of recognition of the body's own cells and tissues by the immune system. MHC class II molecules are expressed on cells of the immune system and present foreign antigens to CD4+ T-helper cells, contributing to anti-pathogen immunity.

It is important to match HLA genotypes between donor and recipient, as a rejection of the graft would occur otherwise, if the recipient's own lymphocytes recognise the donor's stem cells as foreign and attack them. If transplants are matched only partially, a stronger post-transplantation immune suppression in the recipient will be required.

Apart from the MHC antigens, minor histocompatibility antigens (mHA) also play an important role in the differentiation between host and donor cells. The mHA are peptides derived from an individual's own degraded proteins presented by the MHC class I molecules and usually differ between the donor and recipient. These mHA antigens induce a graft-versus-leukaemia (GvL) effect, when donor T-lymphocytes recognize and kill leukaemic stem cells of the recipient. This means a more efficient curative effect may be achieved by allogeneic HSCT, which also explains lower relapse rates compared to autologous and syngeneic HSCT: while with any type of transplantation cancer stem cells may remain viable in the bone marrow after chemotherapy, with allogeneic transplantation they are later eradicated by the donor immune cells. However, when donor lymphocytes attack healthy cells of the recipient, it may lead to the graft-versus-host disease (GvHD) – a severe inflammation of many organs. Excessive production of cytokines, associated with pre-transplantation conditioning, contributes to the GvHD.

Outlook for HSCT

More than 25 000 HSCTs are performed annually. Twenty million volunteer stem cell donors are now registered, which greatly increases the chances of finding an HLA-matched donor for almost every patient. Transplantation mortality and morbidity rates have decreased significantly due to improved conditioning regimens, HLA typing, supportive care, and prevention and treatment of infections. The age of the patients eligible for and benefiting from HSCT has increased over the years. The procedure is now also used to cure more advanced disease stages. It is predicted that the number of HSCTs will continue to increase in future, especially using stem cells from mobilised peripheral blood and perhaps umbilical cord blood too.

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Useful links

www.ebmt.org
The European Group for Blood and Marrow Transplantation

www.cibmtr.org
Center for International Blood and Marrow Transplant Research (CIBMTR)

www.asbmt.org
American Society for Blood and Marrow Transplantation (ASMBT)

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