MYELOMA CANADA
MAKING MYELOMA MATTER

InfoSheet

ALLOGENEIC STEM CELL TRANSPLANTATION (SCT) & GRAFT-VERSUS-HOST DISEASE (GVHD)

Overview of allogeneic SCT and its indications

Allogeneic SCT is characterized by the transfer of hematopoietic stem cells (graft) from a donor to another person. The donor's stem cells must be as compatible as possible with the recipient's compatibility antigens. This approach is not standard for treating myeloma, since it carries a higher level of toxicity and a greater risk of complications when compared to autologous SCT where the donor of the stem cells is the person who receives them. Thus, allogeneic SCT will generally only be undertaken under the supervision of a clinical trial.

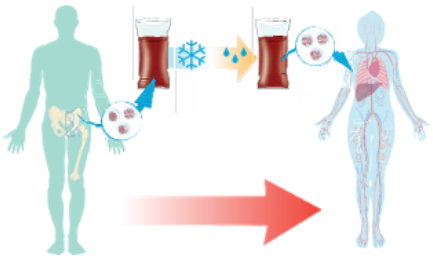


Figure 1 : Allogeneic (donor) stem cell transplant. HighDoseTherapyAutoloStemCellTransp_Infoguide_MyelomaCan_30April2019_fr.indd Spread 11 of 26 - Pages(37, 6)

Statistics

Approximately 1,000 allogeneic stem cell transplants are performed each year in Canada. Approximately 50% of allograft patients will develop graft-versus-host disease (GVHD)[1], which remains the main cause of morbidity[2]. The mortality rate may also appear high, ranging from 17% to 20% among allogeneic SCT recipients who contract GVHD[3].

[1] Iaglowski SM, Devine SM. *Curr Opin Hematol.* 2014;21(2):141-147
[2] Ferrara JL, et al. *Lancet.* 2009;373(9674):1550-1561.
[3] Pasquini MC, Zhu X. http://www.cibmtr.org. Consulted May 13, 2016.

Indication

Allogeneic SCT is considered for patients with unfavourable genetic or prognostic factors that indicate a higher risk of relapse or of being refractory to standard treatments and autologous SCT. Although offered in greater numbers to younger patients (aged between 40-64), the number of myeloma patients over the age of 65 with access to allogeneic SCT is steadily increasing because of the reduced intensity of conditioning regimens.

Origin of donor stem cells

- Bone marrow
- Peripheral blood
- Umbilical cord blood

Stem cell transplant procedure

The most common way of collecting stem cells from a donor is from their peripheral blood. Stem cells circulating in the blood are collected by a specialized machine called an apheresis machine. The collected stem cells can be used immediately after collection, or frozen and stored until they are injected into the recipient via a catheter.

- Steps (for the recipient):
  - Conditioning with chemotherapy and with/without radiation therapy. This step prepares the body to receive the stem cells and helps control the disease.
  - Grafting (Day 0) is the moment when stem cells are infused.
  - Observation of possible complications (three main types): 1) from conditioning; 2) effects of aplasia (period during which the neutrophils that fight bacteria after the transplant will be at zero); and 3) GVHD, which is an immunological complication that can occur with allogeneic SCT.

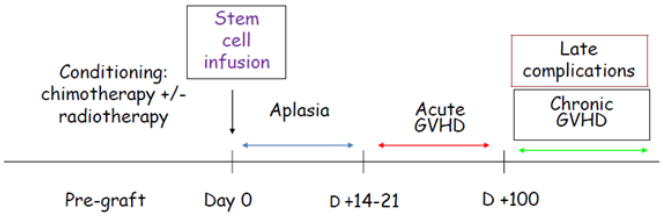
Potential immunological complications

- Graft rejection: destruction of donor cells by the recipient's immune system. Requires a rapid second transplant.
- Acute GVHD : rapidly-onset syndrome involving 3 main organs: skin, digestive tract and liver.
- Chronic GVHD: a slow-onset syndrome that can affect ALL organs, but especially mucous membranes (eyes, mouth, genitals).
- Graft take syndrome: fever, skin rash, diarrhea, increased liver enzymes caused by the release of inflammatory products (cytokines).

What is GVHD, acute GVHD and what causes it?

GVHD is a reaction following an allogeneic SCT wherein the donor's immune system cells attack some of the recipient's healthy cells because they are perceived as a foreign body. The recipient's immune system is weakened as a result of the conditioning regimen, and is unable to defend itself. The donor cells attack the recipient's cells, causing damage to the skin, digestive tract and liver. The severity of symptoms can be assessed according to the extent of skin rash, the amount of diarrhea produced in 24 hours, and bilirubin levels. Biopsies will then be analyzed by a pathologist to confirm the diagnosis.

The term 'acute' is used to indicate that symptoms occur rapidly in the patient. This reaction generally occurs between the time of transplantation (between Day 14 and 21) and Day 100 after allografting.



Standard and supportive treatments

The GVHD incidence is lower when anti-lymphocyte serum (ATG) is used before allogeneic SCT; among other things, it helps limit the severity of lung damage (pulmonary fibrosis). After transplantation, cyclosporine or tacrolimus with small doses of methotrexate are most often used for prevention. On the other hand, different options such as high-dose cyclophosphamide can be used in certain cases, such as haplo-identical transplants with significant mismatches.

Topical treatments (cortisone ointments or creams) are available for minor skin involvement. Corticosteroids (e.g. prednisone) are the most common treatment for digestive involvement, but around 50% of patients who are refractory to them will require further treatment. One treatment option for patients who do not respond to steroids is the administration of ruxolitinib with good results.

Supportive treatments are also necessary to ensure adequate caloric intake to combat tissue damage. These include intravenous nutrition and monitoring for infections and immunosuppressant side effects.

What is chronic GvHD and what causes it?

Chronic GVHD occurs slowly, quietly and later, usually after Day 100 following allogeneic SCT. It is the most frequent late complication after allogeneic SCT, and is most often associated with malfunction of the new immune system. It is a heterogeneous disease in which a single gene can determine multiple traits. It is characterized by inflammatory then fibrotic side effects that can frequently lead to severe or irreversible damage to various organs, notably to the:

- lungs (fibrosis)
- genital tract
- digestive tract
- joints
- mouth
- liver
- eyes
- skin

Standard and supportive treatments

Treatments are adapted to the severity of the complication and the patient's condition. Local or topical treatments are used for mild cases. Otherwise, the most common treatment is once again the administration of corticosteroids such as prednisone, as well as immunosuppressants such as tacrolimus and cyclosporine. Unlike the higher dose offered in the case of acute GVHD in order to better control this serious complication rapidly, when it is chronic, a lower dose is sufficient. In the event of resistance to corticosteroids, second- or third-line treatment should be considered. In particular, ruxolitinib, ibrutinib and belumosudil are treatments approved by both the FDA and Health Canada for patients refractory to corticosteroids.

Supportive treatments include: monitoring of infections and side effects of immunosuppressants, treatment of dry eyes, prevention of cavities, physiotherapy, gynecological examination in women, pancreatic enzymes and monitoring of secondary cancers.

For more information, watch our InfoWebinar at www.youtube.com/@myelomacanada.

Myeloma Canada publications are reviewed by healthcare professionals prior to publication. We thank Dr. Jean Roy for his contribution. The information contained herein is not intended to replace the advice of healthcare professionals.