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TRANSFUSIONAL SUPPORT IN HSCT

Andrea Tiemi Kondo¹, Karen Lima Prata^{2,3}, Aline Miranda de Souza⁴, Sanny Marcele da Costa Lira⁴, Andreza Alice Feitosa Ribeiro^{5,6,7}

1 Hospital Israelita Albert Einstein – Departamento de Hemoterapia e Terapia Celular - 2 Fundação Hemominas

3 Hospital das Clínicas da Universidade Federal de Minas Gerais - 4 Grupo Gestor de Serviços de Hemoterapia

5 Unidade de Transplante de Medula Óssea do Hospital Israelita Albert Einstein - 6 Unidade de Transplante de Medula Óssea do Instituto Nacional do Câncer - 7 Unidade de Transplante de Medula Óssea do Hospital e Maternidade Brasil

CELL THERAPY AND HEMOTHERAPY CONSENSUS

1. MOBILIZATION AND COLLECTION OF PERIPHERAL HEMATOPOIETIC PROGENITOR CELL (HPC)

The mobilization of CD34+ cells for peripheral blood and the collection of peripheral hematopoietic progenitor cells mobilized by apheresis (HPC-A) is a crucial procedure and has as objective: the collection of an adequate number of HPC, the reduction of complications related to the collection, the prevention of failure and the optimization of available resources. ^[1,2]

ALLOGENEIC TRANSPLANT

Mobilization with growth factor

Use of Filgrastim (G-CSF) in the dose 10ug to 20/kg/day in one or two administrations by subcutaneous route, for 4 to 5 days, with the first collection on day 4 or 5. The last dose should preferably be administered 2 to 3 hours before the collection of the sample for the quantification of CD34+ cells in peripheral blood and 3 to 4 hours before the beginning of the apheresis procedure. ^[1]

The minimum dose of CD34+ cells to be collected and infused should be 2 x 10⁶/kg per transplant. Higher doses lead to faster grafting, on the other hand, very high doses are related to an increased incidence of chronic graft versus host disease (GVHDc). Therefore, the most appropriate target dose with current data varies between 4 and 5 x 10⁶/kg per transplant. ^[1] The collection of allogenic HPC-A should be whenever possible by peripheral venous access.

AUTOLOGOUS TRANSPLANT

Mobilization with growth factor

Filgrastim (G-CSF) at dose 10 to 20ug/kg/day in one or two administrations by subcutaneous route, with the first collection on day 5. ^[1,2] The last dose should be administered about 2 to 3 hours before sample collection for quantification of CD34+ cells in peripheral blood.

Mobilization with chemotherapy

Patients who have no indication for treatment with chemotherapy but who have risk factors or have failed to mobilize with the use of GCS-F can benefit from the association chemotherapy and G-CSF in the mobilization process. In this mobilization, cyclophosphamide (Cy) is usually used at a dose of 2 to 4 grams/m². Other options: vinorelbine 35 mg/m² in single dose or etoposide 375 mg.

Use of plerixafor

Plerixafor can be used in association with G-CSF or chemotherapy + G-CSF regimens, in patients with high risk of failure or with previous history of mobilization failure, at a dose of 0.240 mg/kg of body weight, subcutaneous route the night before the collection, 9 to 12 hours before the quantification of CD34+ cells and apheresis collection. ^[2]

Target dose of CD34+ cells to be collected

The minimum dose of CD34+ cells to be infused should be 2 x 10⁶/kg per transplant. The optimal dose to be collected and infused is 5 x 10⁶/kg per transplant. ^[2]

Mobilization with G-CSF alone leads to a CD34+ cell peak between the 4th and 6th day of use.^[1] For patients mobilized with chemotherapy+ G-CSF this quantification normally starts between the 8th and 10th day after the end of chemotherapy administration, during the hematological recovery phase, when the leukocyte count is over 1000 cells/uL.^[2]

HPC-A Collection (Autologous and Allogeneic)

High volume apheresis (volume of blood processed more than 4 times the patient's volemia) consistently **increases CD34+ collection yield in patients and** improves final stem cell collection. However, electrolyte monitoring and replacement is important to avoid adverse reactions from hypocalcemia or hypopotassemia. In the case of allogeneic unrelated donation, it is recommended that a maximum of 24L be processed in one or two consecutive days of collection in adult patients.^[1] **In pediatric patients**, who weigh less than 15 kg are usually transfused to achieve a target hemoglobin (Hb) of 12g/dL and a platelet count of more than 40,000/uL. The prime of the apheresis kit should be performed with red blood cells if their weigh is less than 20Kg. Prophylactic transfusion of platelets is recommended if the platelet count is less than 30,000/uL and a processing proposal of at least three volemia is proposed.^[2]

2. BONE MARROW (BM) HARVEST

Collection by apheresis has been the most used strategy to obtain progenitor cells for autologous and allogeneic non-apparent transplants, the collection of bone marrow is an alternative collection for donors who do not accept mobilization with G-CSF or do not have adequate venous access. Allogeneic bone marrow collection has a lower incidence of graft versus host disease (GVHD) and should be the first option in patients with aplastic anemia. Bone marrow should not be the preferred source of HPC when cryopreservation is needed. In order to avoid dilution with peripheral blood, it is recommended to perform multiple punctures and aspirate the maximum volume of 5 mls at each puncture. The syringes should be washed with a heparin solution at each aspiration. The volume to be collected should respect the target of 10-15 ml/kg of recipient, not exceeding the volume of 20 ml/kg of donor.^[3] It is recommended to evaluate the need for pre-deposited autologous blood collection in allogeneic BM collections, to avoid donor exposure to allogeneic transfusion.^[4] The recommended cell dose for bone marrow collection is total nucleated cell (TNC) $\geq 3 \times 10^8$ /kg of nucleated cell and it is associated with a lower rate of graft failure. Minimum cell dose recommended is

TNC 2×10^8 /kg.^[4] When red cell removal of bone marrow product is necessary such as due to major ABO incompatibility or if it is cryopreserved, an attempt should be made to collect a larger volume, as there will be a loss of about 20% of the nucleated cells collected with processing.

3. PROCESSING AND CRYOPRESERVATION OF HPC-A

There are two main cryoprotective solutions used in HPC freezing. A) Dimethylsulfoxide (DMSO) associated with a protein source (autologous plasma or human albumin) combined with an equal volume of cells in order to obtain a final DMSO concentration of 10%. B) DMSO associated with hydroxetilamide (HES) and a protein source, usually human albumin, in final concentrations of 5%, 6% and 4%, respectively.^[6,7] Studies indicate that the solution that associates HES with DMSO is superior to the one that uses DMSO alone. EBMT recommends the association of ACD-A cryoprotectant solution at a dose of 0.05 to 0.25 mL per mL of product to reduce the risk of lump formation.^[5]

Regarding the concentration of nucleated cells for cryopreservation of HPC, some centers prefer to perform cryopreservation in low doses, i.e., with the final concentration between 100 and 200 $\times 10^6$ cells/mL.⁸ Other centers have already demonstrated that the final concentration up to 300 $\times 10^6$ cells/mL is safe.⁹ The ideal rate of freezing of HCT is 1 to 2° C per minute. Ideally, equipment should be used that allows freezing of the bags at programmed temperature, but many centers have opted for the use of mechanical freezers at minus 80° C.^[6,10]

Storage

The products can be stored in a mechanical freezer with a temperature between -80° C and -150° C or in tanks containing liquid nitrogen or vapor phase. Storage in freezers at -80° C has been increasingly used, when the transplant will be performed in a few weeks or months after cryopreservation, however there are reports of clinical use of cryopreserved bags with DMSO + HES in freezers at -80° C for up to 4148 days.^[10] Tanks containing liquid nitrogen appear to be safer in maintaining temperature however, additional care is required in this type of storage due to the risk of cross contamination between products.^[11]

4-TRANSPORT, THAWING AND INFUSION OF HPC

The transport must take place in rigid, resistant outer packaging of adequate size to the volume of bags to be transported.

For fresh products: The temperature should be kept between 2 and 24°C positive (preferably close to 4°C). And the total time between the end of the collection and the beginning of the infusion should not exceed 48 hours. For cryopreserved products in a mechanical freezer (-80°C), the temperature must be kept at or below -65°C until the moment of thawing, and for cryopreserved products in nitrogen (-150°C), the bags must be kept at a temperature of less than -130°C.^[12]

Thawing: To reduce the risk of serious adverse events, ideally the maximum DMSO volume is 1ml DMSO/Kg receiver weight/day. If the DMSO volume is higher than this limit, consider dividing the infusion into two or more consecutive days. For pediatric patients, especially those of lower weight, removal of DMSO may reduce the risk of adverse effects.^[13]

Pre medication: The hydration as well as the use of mannitol before the HPC infusion, leads to an increase in diuresis and prevents renal damage caused by the deposit of free hemoglobin present in the product to be infused. Diphenhydramine, dipyrone and hydrocortisone are often administered to prevent allergic, non-hemolytic fevers and/or DMSO-related reactions.^[13]

Thawing: Cryopreserved products should be thawed in a water bath with distilled water or saline at 37°C (+/-1°C). The use of sterile plastic bags during thawing process can help reduce contamination in cases of bag breakage and product leakage.

Infusion: Transfusion equipment without leukocytes filter should be used for infusion and the recommended rate is 10mL/minute for thawed products and 6mL/Kg of receiver weight/hour for fresh products.

Reactions related to DMSO: DMSO is the main cause of adverse events during the infusion of cryopreserved products. The administration of >1ml/kg DMSO in 24 hours is the recommendation for the prevention of adverse events. Patients often report coughing, and taste of preservative during administration, which can be reversed by reducing the infusion rate. Changes in vital signs can be observed such as hypertension, tachycardia or bradycardia.

Cytokine Release Syndrome

Cytokine release syndrome is a systemic inflammatory response syndrome related to immune hyperstimulation or aberrant immune activation, leading to elevated levels of cytokines and inflammation. This complication can present mild symptoms of fever and chills, but it can sometimes lead to severe

conditions with hemodynamic instability, which can culminate in multiple organ failure.^[14] Non-infectious fevers occur in 80% to 90% of haploidentical transplant recipients between days 0 and +6. They usually refer soon after administration of cyclophosphamide and are associated with class II incompatibility and higher CD3 + graft cell dose.^[15]

5-TRANSFUSION SUPPORT IN BONE MARROW TRANSPLANTATION (BMT)

As general recommendation, blood transfusion (RBC concentrates and platelet concentrates) intended for BMT candidate patients should be leukoreduced, i.e., contain less than 5.0×10^6 leukocytes per unit aiming at preventing non-hemolytic febrile reaction and anti-HLA alloimmunization. For prevention of CMV, the recommendation is leukoreduction or the use of blood products from seronegative donors for CMV.^[16]

In addition, these blood components and granulocyte concentrates should be irradiated to prevent transfusional GVHD.^[17] The duration of use of irradiated products should be based on the time of immune reconstitution of the patient and in general for autologous BMT should be initiated at least 2 weeks before collection of HPC and extend to 3 months after transplantation and for allogeneic BMT at least before the onset of conditioning to 6 months after transplantation.

SPECIAL SITUATIONS

1. Platelet Refractory (RP)

Patients submitted to BMT may develop platelet refractoriness after repeated transfusions of allogeneic platelet concentrates. Their causes may be non-immune (> 80% of cases) and immune (< 20% of cases).¹⁸

The diagnosis can be confirmed by calculation of platelet increment (CCI) after transfusion of recent platelets (< 48 hours of collection), identical ABO verified in two different and preferably subsequent moments. ICC values below 5000/ μ l collected between 15 minutes and 1 hour after transfusion (1hour ICC) or ICC values below 2500/ μ l collected between^[18] and 24 hours after transfusion (24hour ICC) define the case as platelet refractory.

The management of PR involves the suspension of non-immune factors, when possible, the research of anti-HLA class I antibodies which is responsible for 80% of the cases of immune PR, in addition to the

cross-examination with patient serum. In immune PR it is recommended the use of platelet concentrate compatible with the antibody identified in the receptor^[19], ideally compatible with the four antigens (HLA-A and HLA-B). When the response is unsatisfactory other causes such as anti-HPA or non-immune factors should be investigated.

2.Granulocyte transfusion

Granulocyte transfusion is used to prevent infections in patients with neutropenia or neutrophil function disorders ^[20] and to treat severe neutropenia (granulocytes < 500/μL) associated with bacterial and fungal infections that are not responsive to appropriate antibiotic therapy and of broad spectrum. However, there are still no randomized studies that prove its clinical efficacy in treating infections and that demonstrate improved survival.^[20,21]

The process for granulocyte transfusion requires some care with the donor, product, and recipient. In general, candidates for donation must follow the

same clinical criteria of suitability as a conventional blood donation, have carried out laboratory screening for infectious diseases transmissible by blood within 72 hours of collection and receive mobilizing agents (corticosteroids and G-CSF) at least 12 hours before collection. The granulocyte concentrate collected by apheresis, must contain above 1x10¹⁰ leukocytes/unit/dose for an adult recipient and have ABO compatibility respected. It should be infused irradiated and as soon as possible after the collection is completed.^[22]

6-ALLOGENEIC BMT WITH ABO INCOMPATIBILITY

Approximately 30% of allogenic related transplants and 50% of unrelated transplants will have some degree of ABO incompatibility.

The main immuno-hematological consequences of ABO-incompatible transplants are summarized in **table 2**.

TABLE 2 - Immuno-hematological consequences of ABO TCTH incompatible

ABOIncompatibility	Consequences	Causes
Major	Acute hemolytic response	Infusion of incompatible red blood cell
	Delay in the grafting of granulocytes and platelets	Loss of progenitor cells hematopoietic in the process of RBC removal of the product.
	Delay in erythroid grafting	Presence of isoagglutinin anti d-nor
	Pure aplasia of red series	Persistence of anti-donor isoagglutinin.
Minor	Acute hemolysis	High isoagglutinin titres in donor plasma
	Late hemolytic reaction	Donor B lymphocytes producing anti-receptor isoagglutinin (passage lymphocyte syndrome)

CONDUCT TO MINIMIZE THE RISKS OF INFUSION:

The risks of infusion of the product with ABO incompatibility can be minimized by manipulation of the graft associated or not with measures to reduce the anti-donor iso-hemagglutinins circulating in the recipient and by adequate hemotherapeutic support.

TABLE 3 - Procedures for handling TCPH with ABO incompatibility. Modified from Worel, 2016

ABO incompatibility	Grafting manipulation	Receiver care
Major		
Receiver with titre of iso-hemagglutinin anti-donor \geq 1:32	HPC-BM RBC removal of product	- Infusion of plasma with donor ABO type - Therapeutic Plasmapheresis - Proper hemotherapeutic support
	HPC-A < 20 mL red cells: infusion without manipulation \geq 20 mL red cells: desferitrocitation	
Receiver with titre of iso-hemagglutinin anti-donor \leq 1:16	HPC-BM RBC removal* HPC-A Infusion without manipulation	Proper hemotherapeutic support
Minor		
Donor with iso-hemagglutinin titre anti receiver \geq 1:256	HPC-BM or HPC-A Plasma removal	Proper hemotherapeutic support
Donor with iso-hemagglutinin titre anti receiver \leq 1:128	HPC-BM Plasma removal	Proper hemotherapeutic support
	HPC-A Infusion without manipulation	

* Some centers have opted for infusion without manipulating the graft. **HPC-A** = hematopoietic progenitor cells of mobilized peripheral blood collected by apheresis; **HPC-BM** = hematopoietic progenitor cells from bone marrow.

Red blood cell removal

It consists of the process of removing erythrocytes from the product to be infused. It can be manual or automated, however, to minimize the costs of the process, most services use the manual technique, with the help of a sediment agent, usually the hydroxyethyl starch (HES) at 6% of high molecular weight, added to the product in the proportion 1:4 to 1:8. There is no consensus on the maximum volume of red blood cells to be safely infused. Most ser-

vices limit this volume to 10 to 40 mL for adults. In pediatrics, some authors recommend transfusion of up to 0.4 mL/Kg and others consider infusion of up to 3mL/Kg safe.^[24]

Plasma Removal

Removal of excess plasma from the product by centrifugation (400 to 4000xg for 10 to 20 minutes). The cellular loss in this process is usually less than 5%.

Reduction of the isoheмоagglutinins anti donor of the receiver

It is possible to reduce the titration of the anti-donor isoheмоagglutinins circulating in the receptor by means of therapeutic plasmapheresis or by infusion of secretory plasma, AB or isogroup with the donor.^[25,26] The American Society of Apheresis (ASFA) considers the indication of plasmapheresis in BMT with ABO major or bidirectional incompatibility as category II with GRADE 1B for HPC-BM and GRADE 2B for HPC-A and guides the performance of the procedure before the infusion of the graft, with human plasma or albumin or a combination of these.

7 – DONOR LYMPHOCYTE INFUSION (ILD)

Infusion of donor lymphocytes (ILD) may be requested in cases of relapse of disease, reduction of chemotherapy, viral infections difficult to control, among others.^[27] The efficacy of lymphocyte infusion varies according to the type and volume of the underlying disease, leading to 70-80% complete response in cases of cytogenetic or hematologic relapse of acute myeloid leukemia (CML) while less than 40% of patients with recurrent acute leukemia respond to the ILD.^[28]

Donor evaluation:

The medical evaluation of the donor prior to the collection of lymphocytes is mandatory under current legislation and the eligibility criteria are the same used for blood donors, and serology for cytomegalovirus (CMV).

Lymphocyte collection:

Lymphocytes can be obtained from the buffy coat of whole blood, however, the collection through apheresis equipment can offer a greater amount of CD3+ cells and is the most used. For the apheresis cell collection process, an adequate venous access should be obtained and the need for central venous catheter implantation should be avoided. Each apheresis session should process 2 to 2.5 volemia and if the number of cells needed is not obtained, a second procedure can be performed.^[29]

Donor Mobilization:

There is no need for any medication to collect lymphocytes from the donor, however, when the ILD is programmed (prophylactic) or highly probable, a small aliquot of the product obtained for CTH collection for transplantation can be separated.

Some studies show that previous use of G-CSF promotes T cell hyperresponsiveness, with polarization

to the Th2 strain, induction of regulatory T cells and tolerogenic dendritic cells, which reduces the risk of graft disease against the host and maintains the benefits of graft cells against the disease^[30]. Some centers choose to use CD3+ cells obtained on the day of CTH collection for transplantation, as long as the collection was by apheresis,

Storage of collected cells:

The collected cells should be kept refrigerated and preferably transfused as soon as possible after collection in case of fresh infusion.

Doses and treatment schemes:

The dose of lymphocytes to be infused depends on the type of BMT, patient or disease, and should be defined by the transplant team taking into consideration the potential risk of GVHD, as well as the aggressiveness of the disease to be treated. Patients at higher risk of developing GVHD, such as those undergoing haploidentical transplantation, can start infusions with a low dose : 1 x 10⁵ CD3+/Kg cells from the recipient for preemptive use.^[31]

.For therapeutic use, a staggered dose regimen starting with the 1 x 10⁶ Cd3+/Kg dose of the recipient, and subsequent doses of 5 x 10⁶, 1 x 10⁷, 5 x 10⁷ Cd3+/Kg cells of the recipient is the most commonly used. The interval between doses can vary from 3 weeks to 3 months and, as well as the dose increase, will depend on the response of the patient and the degree of graft disease against the host.^[30,31]

8-ANTI-HLA DONOR DESENSITIZATION PROTOCOLS WITH HLA INCOMPATIBILITY.

The presence of donor-specific anti-HLA antibody (HLA De) is associated with grafting failure.^[32] Research for these antibodies is indicated for partial HLA compatible transplants and haploidentical transplants. The risk of grafting failure depends on the level of antibodies detected and the properties this antibody presents. Polytransfused and multiparous patients are more likely to present antibodies. Whenever possible, another donor should be tried for which the patient does not present anti-HLA De antibody.^[33]

The presence of anti-HLA De antibodies with MFI (Mean Fluorescence Intensity) above 2000 is an indication of desensitization protocols to reduce or eliminate these antibodies, which should be discussed among BMT team, chemotherapy team and histocompatibility laboratory. The strategies involve:

Depletion of antibody producing cells: a) use of rituximab (action on B lymphocytes): (375mg/m²) 1 day after intravenous immunoglobulin; b) Bortezomib (action on plasma cells): optional medication, being done 3-4 applications before starting plasmapheresis, therefore about 3 weeks before the start of conditioning.

Reduction of antibodies already formed - plasmapheresis: generally 3 sessions with exchange of 1.5 plasma volume and replacement of 100% volume with 5% albumin before starting the conditioning. It cannot be performed during conditioning or on D+3 and D+4 when the cyclophosphamide is infused in haploid transplants. Another plasmapheresis session can be performed on D-1 if anti-HLA antibodies persist until this preterm and strategy phase.

Neutralization of antibodies with: a) Intravenous immunoglobulin (IgEV): 1 g/kg performed one day after the last session of plasmapheresis; b) infusion of leukocytes irradiated from the donor ("buffy coat"): obtained from a unit of whole blood from the donor collected in D-2, about 40-50 ml of buffy coat is administered the day before the infusion. The inclusion of this technique has obtained good results, even when the use of plasmapheresis and EV immunoglobulin has not decreased or eliminated the Anti- HLA De antibodies. An option to obtain the buffy coat of whole blood is the use of 40 ml of the bag of hematopoietic peripheral blood progenitor cells collected 1 day before the infusion.^[34]

The combination and number of strategies used will depend on the risk and level of anti- HLAe antibodies. Some factors are considered additional risks: presence of multiple antibodies, presence of the same anti-HLA mismatch from a previous transplant and son-to-mother donation.^[34] The reduction of anti-HLA antibodies and should be monitored during the protocol: after the plasmapheresis, before starting the conditioning and before the infusion of hematopoietic progenitor cells and after the infusion. Patients may have increased levels of anti-HLA antibodies on D-1 (rebound), in which case 1 or 2 additional sessions of plasmapheresis and/or intravenous immunoglobulin may be performed on D+1 and D+2 days. The choice protocol should take into account the risk of graft failure, higher than those with anti-HLA antibody >5000 MFI and antibody persistence during conditioning. Use of buffy coat should be considered in patients with very high levels of MFI or persistence of antibodies after other techniques used.

9-INDICATION OF PHLEBOTOMY IN IRON OVERLOAD POS BMT

After the transplant, patients may have iron overload due to transfusion support, which will not be eliminated without therapeutic intervention. Results from studies on the impact of iron overload on thalassemia and the normal population indicate the need for normal iron levels in the post TMO period. In the chaos with ferritin above 2500ug/L, transferrin saturation close to 100%, there is a high risk of liver damage and irreversible tissue damage.^[35]

With erythropoiesis re-established after a successful transplant, phlebotomy is a therapeutic option to drug treatment, being a safe, effective, low cost alternative, but only applicable to patients with sustained hematopoiesis, and cannot be used in the immediate phases of transplant. Iron chelators can be used, but it is a more expensive alternative and requires care due to renal toxicity, when used in conjunction with cyclosporine.^[36]

10 – ACCREDITATION OF HEMOTHERAPY AND CELL THERAPY SERVICES

Any health care, especially the more complex ones such as haematopoietic stem cell transplantation and other forms of cell therapy, needs some elements to achieve good health care, such as: registration of activities that make it possible to identify improvements in care and research practice; implementation and monitoring of practices based on quality standards and reporting and dissemination of treatment results applied to patients.³⁷ Although hematopoietic stem cell transplantation has

evolved a lot in the last 50 years, this procedure is still associated with high morbidity and mortality.³⁸ Another aspect that requires much attention is the use of healthy donors, family or not, in the therapeutic process.

Internationally, there are 2 organizations that have defined standards and accreditations in these 3 areas: FACT (Foundation for the Accreditation of Cellular Therapy) in the United States of America founded in 1996 and JACIE (Joint Accreditation Committee of ISCT) , founded in 1999 by ISCT and EBMT.

Generally the patterns of operation are defined in three major areas: 1- collection of cells for transplantation or cell therapy; 2- laboratory processing, storage, distribution and infusion of hematopoietic cells and 3- clinical part of patient care during the transplantation period. The requests can be partial for all

3 areas or separately: be global for adults and pediatrics or separately. In all 3 sessions are addressed aspects such as requirements for the facilities; training of personnel and training; quality control of inputs used; control of updating and implementation of technical procedures; evaluation, selection and care of the donor; databases and registration, and

items appropriate to each session. The continuous evaluation of the program performance is based on the analysis of specific indicators such as morbidity, mortality, incidence of adverse events in the area and the reporting of data to National Centers, for example, RBT and International (CIBMTR).³⁸

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