Hematopoietic Progenitor Cells (HPC), Cord Blood

This product information addresses:
- HPC, Cord Blood.

Introduction

This Circular of Information is an extension of the product container label for minimally manipulated unrelated cord blood units, HPC, Cord Blood. The Circular of Information provides general information to the Transplant Centres (TCs) that administer HPC, Cord Blood.

This product, its labeling, and the process by which it was manufactured and distributed, conform to the Safety of Human Cells, Tissues and Organs for Transplantation Regulations, issued by Health Canada.

Composition and properties

HPC, Cord Blood contains hematopoietic progenitor cells collected from the umbilical cord and placenta immediately after delivery of a baby. The cord blood is collected by gravity drainage into a sterile cord blood collection bag that contains a maximum of 29 mL of citrate phosphate dextrose (CPD) anticoagulant. The cord blood is buffy coat enriched (red cell and plasma reduced) by centrifugation with Hydroxyl Ethyl Starch (HES) prior to controlled rate freezing. The cryopreservation solution is 10% dimethyl sulfoxide (DMSO) and 1% Dextran 40. The HPC, Cord Blood product is processed and cryopreserved within 48 hours of collection. The product is shipped cryopreserved at ≤-150°C in an insulated shipping container (dry shipper) to the TC. The cryopreserved HPC, Cord Blood product in the Canadian Blood Services National Public Cord Blood Bank (NPCBB) is stored in liquid nitrogen at -196°C and does not have an expiry date. The viability and potency of stored products are maintained through our current stability program.

Action

The HPC, Cord Blood product contains hematopoietic progenitor cells, which are capable of repopulating the bone marrow, maintaining a population of self-renewing progenitors, as well as developing into mature cells of the blood and immune system.

Quality Control Criteria

Each HPC, Cord Blood Unit (CBU) contains a minimum of 50 x 10^6 total nucleated cells (TNC) with at least 1.25 x 10^6 viable CD34+ cells and >85% viable nucleated cells at the time of cryopreservation. The precryopreservation nucleated cell content of each unit of HPC, Cord Blood is provided on the final distribution label and accompanying documentation.

Screening of mothers donating their child’s cord blood is performed using the Cord Blood Medical History/Health Assessment Questionnaire, in accordance with the Safety of Human Cells, Tissues and Organs for Transplantation Regulations.

Testing

Prior to cryopreservation, the HPC, Cord Blood is tested for the following:
- ABO group
- Rh type
- Abnormal Hemoglobin
- HLA typing
- Quality Control Testing: Total Nucleated Cell (TNC) count, CD34+ cell content, Viability
- Colony forming unit (CFU) assay testing is performed on a CBU sample post-processing and post-thaw. The CFU testing kits are indicated for “Research Use Only”.

Microbial culture testing is performed on a post-processing by-product sample consisting of plasma and red blood cells. The testing is carried out using a validated BacT/ALERT®3D Microbial Detection System to detect microbial contamination (aerobic bacteria, anaerobic bacteria, and fungus).

Prior to distribution, an attached segment from the CBU is thawed, washed and tested for TNC count, viability and the CFU assay is performed.

A maternal sample has been tested and found non-reactive for:
- Antibodies to human immunodeficiency virus (HIV-1 and HIV-2), hepatitis C virus (HCV), human T-cell lymphotropic virus, type I and II (HTLV-I/II), hepatitis B core antigen (HBsAg)
- Hepatitis B surface antigen (HBsAg)
- Presence of viral RNA [HIV-1, HCV, and West Nile virus (WNV)]
- Presence of viral DNA [hepatitis B virus (HBV)]
- Syphilis
- Cytomegalovirus (CMV) antibodies
- Antibodies to Trypanosoma cruzi (T. cruzi or Chagas Disease) when increased Chagas risk is indicated on the Cord Blood Medical History/Health Assessment Questionnaire.

Delivery, receipt and handling

The HPC, Cord Blood is stored at Canadian Blood Services National Public Cord Blood Bank in liquid nitrogen at -196°C. It is transported to the TC in a tamperproof insulated dry shipper.

All samples (maternal and cord) are stored at ≤-150°C. Samples will be provided to TCs “AS IS” and Canadian Blood Services makes no warranties of merchantability or fitness for a particular purpose or test.
Upon receipt the TC must inspect the dry shipper to ensure:

- The tamper-proof seal is intact.
- It is free of cracks, leaks and excessive condensation.

In the event that the dry shipper is damaged, please contact the OneMatch Stem Cell and Marrow Network immediately. Instructions for contacting the OneMatch Stem Cell and Marrow Network in the event of this or any other concern about the product or container are provided on the accompanying CBU Receipt form.

It is recommended that the TC adhere to the following instructions for receipt and handling of the dry shipper and HPC, Cord Blood product:

- TC must maintain the dry shipper in an upright position.
- TC must handle the dry shipper carefully, avoiding bumps, abrupt movements and extreme storage temperatures.
- To open dry shipper and access cryopreserved product, remove security seal and remove dry shipper lid. Handle the metal cassette containing the HPC, Cord Blood carefully to avoid damaging the product.
- The HPC, Cord Blood product must be removed from the dry shipper for storage at ≤ -150°C.
- TC must follow their institutional safety policies and procedures for handling cryopreserved cellular therapy products.

Indications

The HPC, Cord Blood may be used in the treatment of a wide variety of malignant hematological and non-malignant diseases (e.g. leukemia, lymphoma, multiple myeloma, hemoglobinopathies, inherited metabolic disorders) and post chemotherapy for cancer treatment. Graft-versus-tumor effects may occur and aid in eradicating residual malignant disease in the recipient following unrelated allogeneic HPC, Cord Blood infusion.

Contraindications

Specific contraindications are determined by TC institutional policies and protocols. HPC, Cord Blood may be contraindicated for patients with known intolerance or hypersensitivity to DMSO, CPD, HES, or Dextran-40.

Warnings and precautions

The intended recipient must be properly identified before the infusion is started.

CAREFUL DONOR SELECTION AND AVAILABLE LABORATORY TESTS DO NOT ELIMINATE THE HAZARD OF TRANSMITTING INFECTIOUS DISEASE AGENTS FOR WHICH TESTING IS PERFORMED OR FOR PATHOGENS THAT ARE EITHER NOT RECOGNIZED OR FOR WHICH THERE IS NO DONOR SCREENING TEST.

HPC, Cord Blood may contain residual antibiotics if the cord blood donor was exposed to antibiotics in utero. Patients with a history of allergic reactions to antibiotics should be monitored for allergic reactions following administration of this product. There may be an effect on the reliability of the sterility test results if the cord blood donor was exposed to antibiotics in utero.

The polyvinyl chloride (PVC) used in the collection pack used to collect the cord blood unit complies with the European Pharmacopeia. The collection pack is licensed by Health Canada for use in Canada. The plasticizer is DEHP. HPC, Cord Blood could contain phthalates.

As manufacturing supplies associated with this product are not guaranteed to be latex-free, Canadian Blood Services National Public Cord Blood Bank cannot guarantee that this product is latex free.

Thawing and administration

Wash, reconstitute, thaw, and infuse according to TC institutional safety policies and procedures for handling cryopreserved products. If there is an unexpected delay in administration and the product must be held for later infusion, the OneMatch Stem Cell and Marrow Network should be contacted.

- Once thawed, HPC, Cord Blood product must not be re-cryopreserved.
- TC must infuse thawed product immediately according to local TC policy.
- Employ aseptic technique.
- Do not administer HPC, Cord Blood through a filter designed to remove leukocytes.
- HPC, Cord Blood may be filtered through a 170- to 260-micron filter designed to remove clots or clumps of cellular debris.
- Mix HPC, Cord Blood thoroughly before use.
- Do not irradiate HPC, Cord Blood.
- Do not add or infuse medications or solutions through the same tubing with HPC, Cord Blood with the exception of 0.9% Sodium Chloride, Injection (USP) or facility-approved solutions.
- Observe the patient periodically during and after administration to detect adverse reactions. Monitor patient closely following administration as per TC institutional policies and protocols.
- Record vital signs at minimum before and after administration, or more often if required, as per TC institutional policies and protocols.
- Infusion rate is dependent on clinical factors and the product volume to be administered as per TC institutional policies and protocols.

The OneMatch Stem Cell and Marrow Network tracks all CBU infusions with the assistance of our clinical partners. We require TCs to complete and return the Thawing and Infusion Report form to the OneMatch Stem Cell and Marrow Network as soon as possible.

Errors, accidents, and adverse events

Potential adverse events related to a cord blood infusion range in severity from minor with no sequelae to life-threatening. All adverse events occurring during infusion should be evaluated to determine whether or not the infusion can be safely continued or restarted. All adverse events suspected to be related to an infusion (whether during or after infusion of HPC, Cord Blood) should be reported to the OneMatch Stem Cell and Marrow Network and any applicable regulatory bodies. For further information, refer to the package insert that accompanies this product.
## TABLE 1: The following adverse events have been described with infusion of cord blood products

<table>
<thead>
<tr>
<th>Event</th>
<th>Symptoms and Signs</th>
<th>Etiology</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO toxicity</td>
<td>Cough, flushing, urticaria, hypertension, chest tightness and wheezing, nausea and vomiting, bradycardia and tachycardia.</td>
<td>Caused by residual DMSO in product.</td>
<td>Most common adverse event. May be minimized by washing product or pretreatment with antihistamines.2</td>
</tr>
<tr>
<td>Graft-versus-host disease (GVHD)</td>
<td>May affect skin, liver, lung, bowel, marrow and rarely other organs in varying degrees.</td>
<td>Viable T lymphocytes in CBU product engraft in the recipient and react against tissue antigens in the recipient.</td>
<td>Severely immunocompromised recipients are at greatest risk. May be acute or chronic.</td>
</tr>
<tr>
<td>Allergic</td>
<td>Urticaria, pruritis; rarely facial or glottal edema.</td>
<td>Antibodies present in the donor or recipient plasma interact with atopic substances.</td>
<td>May respond to antihistamines or corticosteroids or epinephrine in severe cases.</td>
</tr>
<tr>
<td>Anaphylactic</td>
<td>Hypotension, bronchospasm, laryngospasm, with associated dyspnea.</td>
<td>IgA deficient patients with anti-IgA antibodies react with IgA in donor plasma. Patients with sensitivity to HES or DMSO in product also at risk.</td>
<td>Treatment includes – supportive care, fluids, corticosteroids, epinephrine; may require cardiorespiratory support.</td>
</tr>
<tr>
<td>Febrile non-hemolytic transfusion reactions (FNHTR)</td>
<td>Fever, (temperature increase of 1°C or more), chills.</td>
<td>Diagnosis of exclusion. A patient with fever should be evaluated for other more serious infusion reactions.</td>
<td>Antipyretics usually provide symptomatic relief.2, 4</td>
</tr>
<tr>
<td>Transfusion associated circulatory overload (TACO)</td>
<td>Pulmonary edema and dyspnea.</td>
<td>Due to excessive volume or excessively rapid infusion rates.</td>
<td>Unlikely due to small CBU volume.2, 4</td>
</tr>
<tr>
<td>Transfusion related acute lung injury (TRALI)</td>
<td>Acute respiratory distress occurs during or within 6 hours of infusion, hypoxia, new onset of hypoxemia, new bilateral lung infiltrates on chest X-ray and no evidence of circulatory overload.</td>
<td>Associated with the presence of leukocyte antibodies in the donor or recipient.</td>
<td>Treatment is supportive.4</td>
</tr>
<tr>
<td>Delayed hemolytic transfusion reactions (HTR)</td>
<td>Unexplained low grade fever, decrease in hemoglobin / hematocrit levels, mild jaundice, positive direct antiglobulin test, elevated lactate dehydrogenase (LDH) or bilirubin2-14 days post infusion.</td>
<td>Usually due to an anamnestic response of previously formed RBC antibodies.</td>
<td>Treatment is supportive.2, 4</td>
</tr>
<tr>
<td>Acute hemolytic transfusion reactions (HTR)</td>
<td>May be immediate including chills, fever, headache, low back pain, facial flushing, chest pain, rapid labored respiration, hypotension, disseminated intravascular coagulation, shock and kidney failure.</td>
<td>Due to ABO incompatibility or infrequently due to rare RBC antibodies. Rarely non immune due to mechanical/osmotic stress.</td>
<td>Treatment is supportive.2, 4</td>
</tr>
<tr>
<td>Bacterial contamination</td>
<td>Fever, chills, vomiting, severe hypotension, sepsis, shock.</td>
<td>Presence of bacteria or endotoxin in product causing infection or sepsis.</td>
<td>Supportive care, evaluation of blood cultures and aggressive therapy with broad spectrum antibiotics. Evaluate remaining product promptly by Gram’s stain and microbial cultures. 2, 4</td>
</tr>
<tr>
<td>Alloimmunization to antigens</td>
<td>Usually asymptomatic and does not cause physiologic changes.</td>
<td>May occur unpredictably after product administration.</td>
<td>Alloimmunization to white cells, platelets or plasma can be detected by specialized testing.</td>
</tr>
<tr>
<td>Transmission of infectious disease</td>
<td>Variable according to infectious disease.</td>
<td>Unrecognized transmission that was not detected using the tests described outlined in the attached circular.</td>
<td>Reporting of suspected cases of infusion-related infections is described in the Canadian Standards Association Z900.1-12, clause 14.2.5, and Z900.2.5-12, clause 14.2.2.8</td>
</tr>
<tr>
<td>Engraftment syndrome</td>
<td>Fever and rash in peri-engraftment period without other cause. Associated weight gain, hypoxemia, and pulmonary infiltrates in the absence of fluid overload or cardiac disease.</td>
<td>Treatment is supportive, steroid and ventilator support may be required.7, 8</td>
<td></td>
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<tr>
<td>Graft failure</td>
<td>Failure to achieve absolute neutrophil count &gt;500/ul by day 42 post-transplant.</td>
<td>Primary cause is immunologic rejection.</td>
<td>May be fatal.7, 8</td>
</tr>
<tr>
<td>Malignancies of donor origin</td>
<td>Post-transplant lymphoproliferative disorder (PTLD), lymphoma-like disease favouring non-nodal sites, or leukemia of donor origin.</td>
<td>Thought to be donor lymphoid cells transformed by Epstein-Barr Virus (EBV).</td>
<td>Consider serial EBV monitoring of high risk groups.7, 8</td>
</tr>
<tr>
<td>Transmission of rare genetic diseases</td>
<td>Variable, depending on condition.</td>
<td>Unrecognized transmission of genetic disease or susceptibility to the development of disease with genetic basis due to abnormal expression or regulation of genes in the cells within the product.</td>
<td>Important clinical manifestations are rare.5, 7</td>
</tr>
</tbody>
</table>
References


The Circular as a whole or in part cannot be considered or interpreted as an expressed or implied warranty of the safety or fitness of the described HPC, Cord Blood when used for its intended purpose. Attention to the specific indications for cellular therapy products is needed to prevent inappropriate infusion.

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