

BC Children's Hospital Apheresis Program



Our Team

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Apheresis is the continuous separation of blood by centrifugation. Blood is separated by force into three separate components with varying densities; these in turn are either collected or exchanged. Apheresis can either be donor (allogenic or autologous) in the case of collecting stem cells, or therapeutic based, where harmful components in the blood are removed. For our purpose, we separate blood by specific gravity into three components: plasma, white blood cells and platelets, and red blood cells.

The apheresis program at BC Children's Hospital (BCCH) performs leukopheresis (removal of white blood cells), plasmapheresis (removal of plasma) and erythrocytapheresis (removal of red blood cells). Our program began in 1991 and over the years we have performed 1723 apheresis procedures. This includes 469 autologous peripheral blood stem cell collections, 15 allogenic peripheral

blood stem cell collections, 23 bone marrow red cell depletions, 17 white blood cell depletions, 144 red blood cell exchanges and 1015 therapeutic plasma exchanges.

Leukopheresis

Three types of leukopheresis procedures are performed at BCCH. Our most common type is hematopoietic peripheral blood stem cell (PBSC) collection (autologous and allogenic). We also do bone marrow processing and white blood cell depletion.

On average, we perform 20 hematopoietic stem cell collections per year. Typically, we perform PBSC collections for patients requiring high dose chemotherapy to ablate the bone marrow, followed by a stem cell rescue (autologous transplant) as per their treatment protocol. When stem cells are re-infused they find their way back into the bone marrow

and repopulate. These patients are then observed until engraftment and recovery occur. Engraftment is defined as an absolute neutrophil count of $> 0.5 \times 10^9/L$ for 3 consecutive days and a platelet count $> 20 \times 10^9/L$ seven days after the last platelet infusion. Certain types of cancer such as neuroblastoma, CNS tumours, and lymphomas may include stem cell harvest with autologous transplant as part of their treatment regime.

Stem cells are derived from progenitor (pluripotent) stem cells. These cells form in the bone marrow and have the capability for unlimited self-renewal and the ability to differentiate into different types of cells. Our goal in apheresis is to harvest these cells. As these stem cells mature they develop into red blood cells, white blood cells or platelets depending on what the body needs at the time. Stem cells can be collected from a person's body by means of PBSC collection or from the bone marrow via a bone marrow harvest.

For PBSC collections, a cell separation machine is used to collect CD34+ pluripotent stem cells. These cells are located in the mononuclear cell line and therefore this cell line is critical for stem cell collection as the peripheral pluripotent CD34+ stem cells separate along with them. During the collection of these cells, the remaining cells, blood and plasma are returned to the patient.

We collect stem cells fairly early in the treatment process in an effort to collect a higher yield of CD34+ cells. The question is how do we optimize our collection efficiency to obtain this high yield of cells? After chemotherapy is administered, mobilizing agents such as Granulocyte colony stimulating factor (G-CSF) and/or Plerixafor will be given to the patients to encourage the production of stem cells. Peripheral blood counts are then monitored closely by the apheresis director and the apheresis nurse coordinator to time the procedure when the peripheral CD34+ stem cell count is optimal. The patient is then connected to the cell separator either through a central venous catheter (medcomp or short term hemodialysis catheter) or peripherally. At BCCH, an amazing immunology staff that work closely with us, allowing us to monitor counts, providing mid-run CD34+ enumeration so we can ideally collect the targeted transplant dose in one collection. The procedure typically takes 2-4 hours depending on how long it takes to process 3-5 times the patients total blood volume through the cell separator. These cells are collected into a specific type of infusion bag for cryopreservation and are frozen until day 0 transplant.

Patients with major ABO incompatibility to donor bone marrow or stem cell, the apheresis team is able to red cell deplete these products to less than 5% red cells in an effort to minimize acute hemolysis. The procedure isolates the light density stem cells from the bone marrow with minimal red cell and granulocyte contamination. Those cells are collected and immediately transfused to the transplant recipient once the collection has occurred. This type of procedure is referred to as bone marrow processing.

White blood cell (WBC) depletion procedures are the rapid removal of elevated white

blood cells (concentration $>100 \times 10^3 / \mu\text{L}$), in an effort to reduce morbidity and/or mortality of the patient. This procedure follows the same principles that are used for PBSC collection. However, for WBC depletion, large volumes of cells are removed quickly from the blood and are not targeted to a specific cell line. The goal is to focus on effectively reducing circulating white blood cells.

Erythrocytapheresis

The process of removing red blood cells in circulation and replacing it with donor red blood cells is known as red cell exchange. Our team performs 40 red cell exchange procedures on average throughout the year.

Red cell exchange is a procedure that separates and removes abnormal red blood cells from a patient's blood, replacing the cells with healthy donor red blood cells. This procedure is often done peripherally. In an emergent situation where peripheral access is not an option, the procedure is done through a short term femoral hemodialysis catheter.

Blood is continuously removed from the patient with an 18 gauge needle from one of the veins located in the antecubital fossa. This blood is then separated by centrifugation. The patient's plasma, white cells and platelets are then mixed with donor blood (4-10 units depending on the patient's size) and returned to the patient through another peripheral IV (commonly a 22gauge in the wrist or forearm) in the alternate arm. The blood separated during centrifugation is removed into a waste bag and is not returned to the patient. For some individuals this procedure is only needed once in the case of malaria or carbon monoxide poisoning. In others, such as patients with sickle cell disease, this procedure could be required as often as every four weeks.

Plasmapheresis

Plasma Exchange or "Plex" as it is sometimes referred to is commonly used to treat

autoimmune or immune mediated diseases and disorders. In most cases, 4-6 treatments are required to achieve a response. Plasma exchange removes circulating plasma components such as immunoglobulins, albumin, fibrinogen and other clotting factors, urea, creatinine, and electrolytes. It can also remove alloantibodies, autoimmune antibodies, antigen-antibody complexes, plasma proteins, metabolic waste products and plasma-bound drugs or poisons. These antibodies can attack healthy cells or tissue. Other diseases can cause too much protein to be made, which can slow down the blood flow. Some diseases and illnesses we treat with Plex include Myasthenia gravis, Guillain Barre, acute disseminated encephalomyelitis, Goodpasture's and Wegener's syndrome, thrombotic thrombocytopenic purpura, atypical hemolytic-uremic syndrome, autoimmune hemolytic anemia, and sepsis with multi organ failure.

Plasma exchange is the process of separating blood components through centrifugation. We remove plasma and replace it with either fresh frozen plasma or 5% albumin, sometimes using a combination of both. The determining factor for what product we use is disease or illness specific. In some cases, we remove clotting factors and fibrinogen. If the patient is not able to make more because of their underlying illness we use plasma as the replacement fluid in order to replace the deficit.

As with the other apheresis procedures, parts of the blood: red blood cells, white blood cells and platelets which are not being removed are returned to the patient.

This procedure is commonly done through a short term femoral or jugular hemodialysis catheter due to the multiple number of exchanges the patient may require. In extreme circumstances this procedure can be done peripherally. On average, the apheresis team performs 60 plasma exchanges annually.



Approach to therapy in high-risk neuroblastoma

Dr. Rebecca J Deyell MD MHSc FRCPC

Neuroblastoma is the most common extra-cranial solid tumour of childhood and despite recent advances in therapy, remains the third leading cause of childhood cancer related mortality. With a median age at diagnosis of 17 months, neuroblastoma has an annual age-adjusted incidence rate of 10 per million children younger than 15 years. At BC Children's Hospital, we diagnose between 8 and 12 children with neuroblastoma annually.



Neuroblastoma arises from postganglionic sympathetic neuroblasts, typically involving the adrenal medulla or paraspinal ganglia. Clinical presentations vary from the incidental detection of an isolated adrenal mass in an asymptomatic child to a seriously ill child with widely disseminated disease involving the liver, bone marrow and bones throughout the body. Remarkable clinical heterogeneity is the hallmark of neuroblastoma; not only related to its range of clinical presentations, but also with respect to its underlying biology and response to therapy. A group of young children (<12 months at diagnosis) have a form of neuroblastoma (4S) which actually undergoes spontaneous regression without therapy, despite having disseminated involvement of liver, skin and bone marrow. Unfortunately, on the other end of the spectrum, approximately 50% of children are classified as having high-risk disease at diagnosis on the basis of clinical and biologic characteristics that are independently prognostic of survival including age, stage, histology, *MYCN* amplification status and ploidy. In spite of an increasingly intensive approach to multimodal therapy for these children, risk of relapse remains high and long-term overall survival is still less than 40%. It has become clear that novel, targeted therapeutic approaches are desperately

needed to improve survival outcomes.

At the time of a suspected diagnosis of neuroblastoma, which may be first suspected on an abdominal ultrasound, baseline investigations are conducted to define the extent of disease involvement. As the majority of neuroblastoma are MIBG-avid, children routinely undergo a staging ¹²³I-MIBG scan and co-registered CT for baseline cross-sectional imaging. Those children whose tumours are not MIBG-avid would have a baseline PET/CT scan for staging purposes. Other baseline investigations include urine catecholamines (VMA and HVA), bilateral bone marrow aspirates and biopsies and baseline blood work. For paraspinal tumours with suspected intraspinal extension an MRI of the spine may also be required. A surgical biopsy or resection if feasible, of the primary tumour is typically arranged to confirm the diagnosis and to help risk stratify by providing tumour-specific information like histology categorization, ploidy and *MYCN* amplification status. A central venous catheter for administration of subsequent chemotherapy is often placed at the same time.

The current approach to high-risk neuroblastoma therapy includes an intensive, multimodal treatment regimen consisting of 5 cycles of induction chemotherapy, surgery, high-dose chemotherapy consolidation and autologous stem cell transplant/ rescue (ASCT), radiotherapy and maintenance therapy with isotretinoin and targeted immunotherapy.

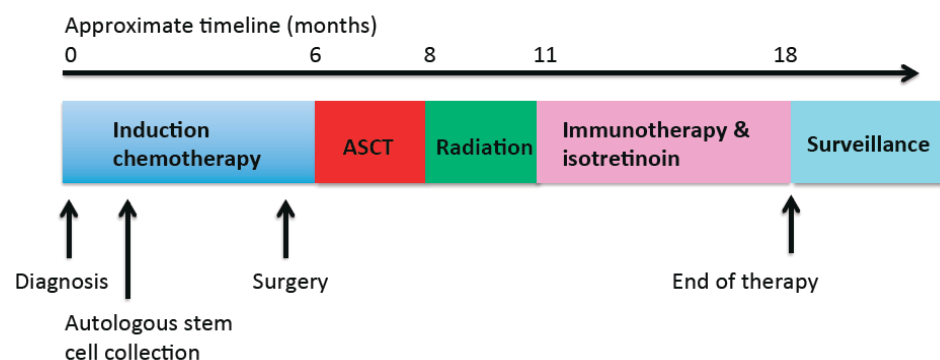
Due to the complexity and intensity of

this therapy, which may extend beyond 18 months, children require extensive supportive care and are at risk for treatment-related morbidity and mortality, along with serious long-term sequelae, such as sensorineural hearing loss. The role of consolidation with myeloablative, high-dose chemotherapy and autologous stem cell transplantation (ASCT) for high-risk neuroblastoma was firmly established in a randomized, phase III pediatric clinical trial. This trial showed improved survival outcomes among children who underwent ASCT versus continuation chemotherapy (5y EFS 30±4% vs 19±3%, p=0.04). In a second randomization, this study also showed that children who received isotretinoin, a differentiation agent, as maintenance therapy after consolidation had significantly improved overall survival. As such, children with high-risk neuroblastoma now routinely undergo peripheral autologous stem cell collection following their second cycle of induction chemotherapy in preparation for consolidation with myeloablative ASCT. The choice of conditioning regimen for consolidation therapy has differed in the North America and European experiences, and the European regimen consisting of busulfan and melphalan is currently being studied in Children's Oncology Group trials.

More recently, targeted immunotherapy during maintenance has been shown to substantially improve EFS and OS for a group of children with high-risk neuroblastoma who have achieved a good response to upfront therapy. A monoclonal

continued on page 4

Figure 1: Approach to Therapy in High-Risk Neuroblastoma



Therapy in high-risk neuroblastoma continued from page 3

antibody directed at GD2, a surface disialoganglioside found on neuroblastoma cells, in combination with cytokines (GM-CSF and IL2) and isotretinoin has been used to further improve survival compared to isotretinoin alone (2y EFS 66±5% vs 46±5%; 2y OS 86±4% vs 75±5%). However, side-effects associated with immunotherapy are significant as more than half of patients experience serious neuropathic pain despite pre-emptive narcotic infusions and almost 25% develop capillary leak syndrome. Efforts are ongoing to further enhance targeted immunotherapy in neuroblastoma in hopes of improving efficacy and decreasing toxicity.

Despite these therapeutic advances for children with high-risk neuroblastoma, the long-term cure rate remains unacceptably low. Up to 15-20% of high-risk patients have

primary refractory disease, for which the standard intensive chemotherapy approach is ineffective. Similarly, children who are diagnosed over the age of 6 years may have a more indolent form of the disease, but ultimately have dismal survival outcomes. As such, novel therapeutic strategies are desperately needed. Targeted radiotherapy using high-dose ¹³¹I-MIBG has been shown to have response rates of approximately 35% in patients with relapsed or refractory, MIBG-avid neuroblastoma. High-dose ¹³¹I-MIBG therapy has recently become available in Canada and is being studied early in therapy for children with primary refractory disease. Myelosuppression is a significant dose-limiting toxicity associated with this therapy and many patients require autologous stem cell reinfusion to facilitate marrow recovery following therapy. Other targeted approaches to therapy are in development, and include the use of small molecule inhibitors of oncogenic drivers.

Inhibition of anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase found to have an important role in both rare familial neuroblastoma cases and in sporadic disease, is being studied in ongoing pediatric clinical trials.

Children diagnosed with high-risk neuroblastoma receive one of the most intensive approaches to multimodal therapy in pediatric oncology practice, in hopes of providing curative therapy for a devastating disease. Autologous stem cell support has a documented role in this therapy, both to facilitate myeloablative, high-dose consolidation chemotherapy and following high-dose ¹³¹I-MIBG therapy, a form of targeted radiotherapy that has an evolving role in the treatment of these children.

For additional reading, please visit National Cancer Institute website: www.cancer.gov/cancertopics/types/neuroblastoma

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PEDIATRIC ONCOLOGY HEMATOLOGY EDUCATION DAY The Pediatric Cancer Trek: Positioning Ourselves for the Future

MAY 8-9, 2014
THU-FRI

BC CHILDREN'S HOSPITAL
CHAN CENTRE FOR FAMILY HEALTH
EDUCATION, VANCOUVER BC



CONFERENCE OVERVIEW

The Provincial Pediatric Oncology Hematology Network, in conjunction with the Division of Pediatric Oncology Hematology BMT, BC Children's Hospital, is committed to provide ongoing educational and discussion opportunities to support physicians and healthcare providers in the care of the child/adolescent with cancer and hematological disorders. This educational day has been developed to reflect the needs of these physicians and multidisciplinary healthcare professionals. There will be opportunity for dialogue, discussion, and questions and answers throughout the program.

TARGET AUDIENCE

- Pediatricians
- Family Physicians
- Pediatric Oncologists
- Pediatric Hematologists
- Other healthcare professionals involved in pediatric cancer care or hematological disorders

PEDIATRIC ONCOLOGY HEMATOLOGY
EDUCATION DAY IS BROUGHT TO YOU BY



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Zach Prince Foundation for
Excellence in Oncology Care

Online registration link <https://events.ubccpd.ca/website/index/110157>

Sickle cell disease: pediatric care in BC

Heather McCartney BSN RN

Sickle cell disease refers to a group of conditions characterized by (1) the presence of sickle red blood cells, and (2) illness that results from the presence of these cells. Sickle cell disease includes, but is not limited to, homozygous sickle cell anemia (Hb SS),



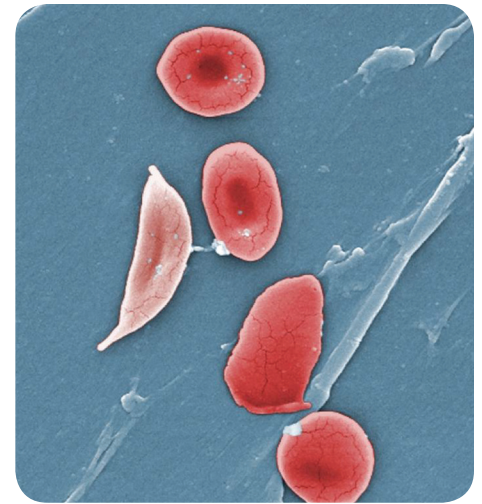
HEATHER
MCCARTNEY

sickle beta thalassemia, and hemoglobin SC disease. In sickle cell disease, a genetic mutation of the beta globin gene causes the production of sickle hemoglobin instead of normal adult hemoglobin. Upon de-oxygenation, rigid polymers form within the sickle cells and change the cell shape to resemble a stiff crescent moon (sickle). Repeated cycles of oxygenation and de-oxygenation weaken the cell membrane and shorten the sickle cell lifespan, causing chronic anemia and functional asplenia at a very early age. The hallmark symptom of sickle cell disease, a vaso-occlusive crisis, occurs when rigid sickle cells get caught on each other and on vessel walls and create blockages in the blood vessels. This reduces blood flow and damages the tissues involved. Pain may or may not be present with a vaso-occlusive crisis, and can be mild (managed at home) to severe (requiring hospital admission). It is important to note that whether or not pain is present, sickling is a continuous process that can cause severe tissue/organ damage over time. Aside from pain, acute complications from sickle cell disease include overwhelming infection from encapsulated bacteria, splenic sequestration, acute chest crisis, priapism, dactylitis and stroke. Patients are also at risk for many serious *chronic* complications, including leg ulcers, avascular necrosis of the joints, osteoporosis, renal and lung dysfunction, pulmonary hypertension and vision and hearing loss.

Because of the complex nature of sickle cell disease and its multi-organ involvement, comprehensive and multidisciplinary care

is required to improve patient quality of life and prognosis. In 2012, the Provincial Blood Coordinating Office (PBCO) created a province-wide initiative called the BC Inherited Bleeding and Red Cell Disorders Services (IBRCD). The IBRCD consists of a pediatric team at BC Children's Hospital (BCCH) and an adult team at St. Paul's Hospital, each with 1-2 hematologists and 2-3 dedicated nurses. These teams provide comprehensive medical care to children and adults with inherited bleeding disorders (coagulopathies) and inherited red cell disorders (hemoglobinopathies) for example, sickle cell disease, across British Columbia (BC).

In BC, comprehensive care for the child with sickle cell disease begins at birth. Newborn screening, introduced in 2009, allows for the prompt referral of new patients to the IBRCD team at BCCH. Early penicillin prophylaxis is initiated, which significantly reduces infant mortality in this population. As the child grows, collaboration with public health units ensures that children with sickle cell are considered asplenic and follow the high risk immunization schedule, including pneumococcal and meningococcal vaccines. Ongoing education is provided to patients and families, and, if requested, to key community players such as daycare providers, teachers and health care providers. Comprehensive guidelines implemented at BCCH ensure regular follow-up appointments and blood work, and guarantee that investigations such as gallbladder ultrasounds, lung function testing, chest x-rays, echocardiograms and vision and hearing testing are done routinely. Should any of these tests identify chronic complications, appropriate referrals are made so treatment can be started to reduce their severity. If the child is eligible, bone marrow transplant from a matched related donor is offered. Hydroxyurea therapy is encouraged for all appropriate patients, and blood work and drug efficacy is monitored closely. Annual transcranial doppler screening identifies patients that are at high risk for stroke. Those considered high risk are offered monthly red blood cell exchanges (erythrocytapheresis). This procedure,



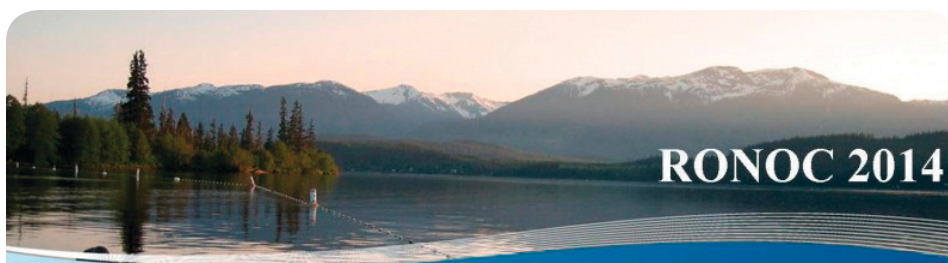
Normal blood cells next to a sickle-blood cell. Colored scanning electron microscope image.

OpenStax College, "Anatomy & Physiology," Connexions, June 19, 2013, <http://cnx.org/content/col11496/1.6/>.

performed by the BCCH Apheresis team, replaces sickle cells with donor red blood cells thus decreasing the child's risk of stroke by up to 90% and reducing the severity of other complications without causing iron overload. If a patient requires a surgical procedure, close collaboration with anesthesia and the surgical department ensures measures are implemented to reduce potential complications. This may include blood work, blood transfusions, red cell exchanges, and intravenous fluids prior to the procedure, and close monitoring for complications afterwards. Finally, patients are prepared to graduate from the pediatric program at 18 years old. Then they are formally transitioned to the adult program at St. Paul's Hospital. This ensures the continuation of comprehensive care as adults.

The IBRCD program is meant to provide hemophilia and hemoglobinopathy patients from across BC with specialized hematological care that compliments and works in collaboration with care from family physicians, pediatricians and community nurses. Referrals for pediatric patients with sickle cell disease or thalassemia can be made to the IBRCD team at BC Children's Hospital using the referral form found at www.bcchildrens.ca/Services/Onc-HemBMT/blood-disorders/default.htm.

Return Undeliverable Canadian Addresses to:
BC Children's Hospital
Provincial Pediatric Oncology/Hematology Network
Attn: Paulina Chen, Network Coordinator
Room A119, 4480 Oak Street
Vancouver, BC V6H 3V4



Realities of Northern Oncology Conference May 2 and 3, 2014 Coast Inn of the North, Prince George, BC

To register <http://ncme.ca/ronoc>

The 15th Annual Balding for Dollars, Main Event: May 10, 2014, 11am-4pm

Child and Family Research Institute Building at BC Children's Hospital
Sign up to cut your hair or "shave for the brave". Everyone is welcome to a "carnival style" day of fun, food, and entertainment.

To register <https://secure.bcchf.ca/SuperheroPages/team.cfm?Event=BFD&Team=7466>

THE PROVINCIAL PEDIATRIC ONCOLOGY/HEMATOLOGY NETWORK

The Network is an interdisciplinary organization whose goal is to ensure appropriate diagnosis, management, follow-up, and end-of-life care for pediatric patients with malignancies and blood disorders.

The Network supports community hospitals and practitioners, and develops partnerships with other healthcare facilities to enable seamless and integrated care for patients and families on treatment and off treatment.

It will further develop and enhance the research programs of basic, translational, and clinical research to better childhood cancer control and improve outcomes for these patients and their families.

FOR MORE INFORMATION

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WELCOME TO THE TEAM FUNDRAISING PAGE OF THE 15TH ANNUAL BALDING FOR DOLLARS MAIN EVENT - MAY 10, 2014

FOUNDATION EVENTS



Our mission is to improve the health and welfare of children in BC with cancer and blood disorders through research, education, and care.