



Pediatric Hereditary Cancer – Opportunities to be Personalized, Proactive, and Preventative

Each year in British Columbia approximately 150 children are diagnosed with cancer. About a quarter of these children are thought to have an inborn genetic predisposition to cancer. Twenty single gene syndromes conferring risk of childhood solid tumours, and a similar number having increased risk of hematopoietic malignancies in children have to date been described. Sometimes a child is the only one in the family with increased cancer risk, other times the predisposition is shared with others in the family. Families are working with oncology and genetics professionals to figure out how we best identify and manage pediatric cancer predisposition syndromes – primary care providers, ophthalmologists, pathologists, oncologists, and geneticists all have a role.

How can diagnosing a syndrome guide a child's cancer care?

Eric's oncologist recognized that while Eric was healthy and developing typically prior to his leukemia, he is of short stature. She therefore engaged the Medical Genetics service to assess the possibility of an underlying genetic syndrome. Eric's chromosomes were studied and found to be fragile, confirming a diagnosis of Fanconi Anemia. This diagnosis will guide aspects of his leukemia care, his future surveillance, and potentially lead to identification of affected family members. In planning Eric's bone marrow transplant, for example, special considerations will include but are not limited to:

- Modification to the conditioning regime (radiation free) and approach to donor graft preparation to minimize risk of subsequent solid tumours.

- Testing potential sibling donors for Fanconi Anemia so that Eric is not offered a donation with genetic risks of another leukemia or other Fanconi Anemia complications. Each sibling of an affected individual has a 25% chance of also having Fanconi Anemia.

Implications to a child's cancer care depend on the specific genetic predisposition syndrome.

Is it useful to identify at-risk children before they develop a cancer?

Alice was born with Multiple Endocrine Neoplasia syndrome 2A, which is associated with a 95% risk of medullary thyroid carcinoma. Knowledge of this allows for prophylactic removal of her thyroid, and avoidance of the life-threatening cancer.

There are established risk management guidelines for the majority of the hereditary cancer syndromes that predispose to solid tumours in childhood and some of the syndromes with hematological risks. Most management focuses on surveillance for early detection, some on prophylactic removal of tissues at risk.

Which of the 150 children diagnosed with cancer this year have a syndrome?

Bella, Cheng and Davinder were all recently diagnosed with brain tumours.

- Bella had a choroid plexus tumour, and based solely on her tumour type, she should be offered genetic testing for Li Fraumeni syndrome.



Dr. Linlea Armstrong MD, FRCPC, FCCMG, Medical Geneticist, Provincial Medical Genetics Programme (left) and Dr. Katherine Blood MD PhD, Medical Genetics and Genomics Resident

- Cheng had a medulloblastoma and meets clinical diagnostic criteria for Li Fraumeni syndrome because her father and grandmother respectively had sarcoma and early breast cancer.
- Davinder also had a medulloblastoma, but in the absence of any personal or family history or associated features a genetic predisposition is unlikely. He is not referred to Medical Genetics.

Whether a child should be referred to Medical Genetics for assessment of a possible genetic predisposition to cancer depends on what the chance of a diagnosis is and how useful it could be to make a diagnosis. There are some tumour types that are so unlikely outside the context of a genetic predisposition that a diagnosis is a significant flag to the possibility. Other times, the presence of a suggestive history of previous cancers in the person or their close relatives warrants careful review. Still other possible clues to watch for are an atypically young diagnosis of the cancer and/or additional non-cancer feature, such as atypical growth or developmental patterns, asymmetries or skin pigmentary abnormalities. *continued on page 2*

How can we identify at-risk children before a first cancer occurs?

Baby Fred has asymmetry of the legs and feet. His family doctor referred him to Medical Genetics for assessment. He was diagnosed with hemihyperplasia (an abnormality of cell proliferation leading to asymmetric overgrowth). Genetic testing demonstrated similar changes as seen in Beckwith Wiedemann syndrome (BWS), indicating his presentation represents the subtle end of the BWS clinical spectrum. He should have surveillance as per BWS.

Some hereditary cancer syndromes have associated physical and developmental manifestations which may be the signs of a syndrome diagnosis. For example, BWS is variably characterized by macrosomia or hemihyperplasia, macroglossia, omphalocele and neonatal hypoglycemia. This syndrome is associated with an increased risk for embryonal tumours, particularly Wilms tumour and hepatoblastoma, but also rhabdomyosarcoma, neuroblastoma and adrenocortical carcinoma. Surveillance is recommended.

Another way which can result in a child being diagnosed with a cancer predisposition syndrome before developing a first tumour is based on a diagnosis of a hereditary cancer syndrome in the family member. Children often come to attention when a parent develops a medullary thyroid cancer and is found to have a pathogenic variant in the gene associated with MEN2.

How does the inheritance within a family work?

Hariet was diagnosed with a rhabdoid tumour. In a percentage of families, siblings have a very high risk of rhabdoid tumour. Careful planning at the time of Hariet's

surgery meant that a tiny part of her tumour could be tested and the mutations which drove formation of her tumour identified. Further testing is then able to clarify where the mutations started. When the mutations are only present in the tumour and not the child's blood, the child does not have an inherited syndrome. If the child shows one of the tumour mutations also in the blood cells, this is evidence that the child has the rhabdoid tumour predisposition syndrome. When that is the case, the mutation could be new in the patient or inherited from one of the parents. It is in this latter scenario that there is a chance of recurrence in siblings.

Knowledge of the inheritance patterns and gene(s) involved in each syndrome, respectively, allows for genetic counselling about risks and provides possibilities of predictive genetic testing. Some syndromes are inherited in an autosomal dominant manner, meaning that parents with increased predisposition for developing cancer have a 50% chance of passing the risk on to each of their children. If the underlying genetic variant in a family with a predisposition to childhood cancer has been determined, predictive genetic testing for at risk children might be a consideration. If the testing in Hariet's family established that her siblings are at risk, predictive testing to guide surveillance would be an option for each.

What is meant by an "incidentally" identified cancer predisposition?

Ingo was being investigated for intellectual disability with a test that provides a broad assessment of the genome. A pathogenic variant involving the APC gene was found, which identifies that he is at increased risk of colon cancer and risk management is indicated for him and any other family member who also carries the variant.

Identification of a hereditary cancer predisposition can occur secondary to genetic testing performed for an alternative purpose. Chromosome microarray and whole exome sequencing are genetic tests that interrogate the whole or large portions of an individual's genetic information. Chromosome microarray testing is routinely ordered for a variety of indications and provides information about segments of a chromosome that may be present in single or multiple copies, compared to the typical

two copies. Copy number variations may contain genes known to be associated with cancer predisposition. Whole exome sequencing provides information about genetic variation within the coding regions of genes. Incidental identification of mutation in a tumour suppressor gene or oncogene can occur and result in the diagnosis of a cancer predisposition syndrome. Ingo's variant could be a deletion involving the APC gene found on a chromosomal microarray or an APC intragenic mutation found on an exome.

What are some of the social and ethical considerations?

When testing is predictive of an individual's future cancer risk, and has the potential to stratify risks of family members, there is important pretest counselling that needs to occur to ensure informed consent of families. These are important for families and care providers to become aware of, but detailing them is beyond the scope of this piece.

Are there useful resources for professionals who want to learn more?

- The American College of Medical Genetics and Genomics and the National Society of Genetic Counselors have published referral indications for cancer predisposition assessment.
- GeneReviews is a publically available online series of review articles with postings for many of the syndromes.

Summary

Children born with a genetic predisposition to childhood cancer can be identified by various means for the purposes of optimizing their cancer care, and early cancer preventative strategies for the child and any other at-risk family members. Criteria that bring children to attention include one or more of the following: a diagnosis of a tumour type on its own associated with a high risk of an underlying syndrome, physical and developmental manifestations suggestive of a syndrome, a family history of high risk cancer or a diagnosed cancer predisposition syndrome, or an incidental finding in genetic sequencing or chromosome studies. This is a complex area of care where investments in organization of clinical care and research have major potential to improve the wellbeing of children and their families.

Examples of syndromes with childhood brain cancer risk:

Biallelic mismatch repair deficiency
Lynch syndrome
Li Fraumeni syndrome
Nevoid basal cell carcinoma syndrome
Rhabdoid tumour predisposition
Familial adenomatous polyposis
Melanoma astrocytoma syndrome
Tuberous sclerosis

Vaccination in Kids with Cancer

Vaccination for common childhood diseases could be the most important medical advance of the era of modern medicine, with a marked reduction in mortality and morbidity due to common infection agents.



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Diseases such as small pox have been eradicated, and morbidity from infections such as polio are no longer commonplace. Unfortunately, due to misinformation on the internet regarding safety of vaccines, and the fact that people do not remember the morbidity and mortality of the pre-vaccine era, the rates of vaccination have dropped significantly in the Western world and there are now many communities where vaccination rates have dropped below 50%. British Columbia (BC) unfortunately seems to be a leader in geographic areas with extremely low rates of vaccination. In affluent areas of Vancouver, reports show rates of vaccination of two year olds of only 60%. Herd immunity (the immunization rates needed to protect the entire population) requires an immunization rate of 90% in the community. We have entered an era where we no longer have herd immunity in BC and we are seeing the impact of this in pediatric oncology where we have had issues with outbreaks involving our patients in their home community of diseases we have not had to deal with in decades such as measles. Unfortunately, a major impact of the anti-vaccination movement is that the most vulnerable members of our community, including the immunocompromised, can no longer rely on herd immunity to keep them safe. Infections in our population of children during therapy can have devastating effects, especially if occurring at times of severe cytopenia or immunomodulation. In addition, chemotherapy has a very significant effect on the long-term immune memory from vaccination – leading to many of our long term survivors of pediatric cancer no longer

having protection due to waning immunity years post chemotherapy. Therefore, many survivors may feel that they are protected from these infections when outbreaks occur, when in fact their immunity has been long lost. Vaccination is therefore a major focus of our survivorship program, with guidelines on who to vaccinate, when to vaccinate, and what special groups need additional vaccination. In collaboration with our infectious disease colleagues and our public health colleagues at the BCCDC we have updated our approach to immunization recently in BC. Our historical model was to check vaccine antibody titers in survivors at specific time points and to vaccinate when immunity levels dropped below protective levels. However, this approach relies on multiple steps, including remembering to do the antibody levels, and then if low arranging for vaccines to be given. In addition, this assumes we can follow our survivors throughout life into adulthood – and does not capture the immunity lost once they graduate from our follow-up clinics. This has resulted in us changing our approach to vaccination in order to ensure highest rates of protection for our survivors, after a review of the available literature. For the average pediatric cancer survivor, we no longer routinely check vaccine antibody titers, but instead do booster vaccines regardless of antibody status. This article will update some of the evidence for this practice change.

Immune System and Cancer Therapy

Our immune system is comprised of both the cellular and humoral immune systems, and these are both suppressed by cancer and its treatment. Humoral immunity is where antibodies from B-lymphocytes recognize antigens on pathogens. Studies looking at antibody levels in children receiving chemotherapy for leukemia show that IgA and IgM levels drop during therapy, but recover approximately 6 months post therapy completion. Interestingly, IgG levels are typically maintained at normal levels throughout treatment. Therefore, vaccinations that children received prior to therapy often have protective effects for them during chemotherapy. This is why we

check varicella IgG levels at time of new patient diagnosis to know whether a child has protection from varicella (which can be fatal in immunocompromised children) such that we will treat those who are varicella IgG negative with VZIG in case of exposure. The cellular immune system involves T-cells, NK cells and macrophages and is also impacted greatly by chemotherapy and is thought to take longer to recover fully post therapy completion (up to 12 months to fully recover post therapy). Immune reconstitution takes much longer post stem-cell transplantation and therefore we have different rules for the allogeneic stem cell transplant group with regards to timing of vaccination (eg delaying live vaccines until 2 years post transplant).

Vaccination During Therapy

There are two reasons why most vaccines are typically not given during chemotherapy. Live vaccines are avoided as these may cause disease with the vaccine virus strain due to immune dysfunction. Therefore, one must avoid the following vaccines in children who are immunocompromised: oral polio, intranasal influenza (Flumist), oral typhoid, BCG, Yellow Fever, MMR and varicella. Inactivated vaccines are safe to give during chemotherapy, yet are typically deferred until after therapy as they have been shown to be much less effective when given before the immune system has recovered from chemotherapy. There were trials of giving varicella vaccination during maintenance phase of therapy in children with ALL, which showed that the vaccine was generally safe to give and that the immune response in the short term was quite good. However, 20-50% of subjects did develop skin lesions with vaccine strain virus that although did not cause morbidity, it did result in infection control issues in the pediatric oncology clinics. Therefore, it is not standard of care to give varicella vaccination during therapy. The only vaccine that we are typically giving during therapy is the yearly flu shot to protect against influenza. We do recommend this to all our children on treatment and only the inactivated (intramuscular) vaccine should be given and should be given when the

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neutrophil count is above 0.5 (and expected to stay above 0.5 for the next 48 hours, in order to minimize risk of admission in case of fever) and the platelet count is above 50,000. Children under 9 years of age who have never previously had the flu shot are recommended to get a second vaccination at a minimum 4 weeks apart.

Vaccination Post Therapy

There is very limited research to guide how and when to vaccinate children post therapy for cancer. The largest study was performed in the UK in 59 children post treatment for ALL (Patel et al, Clin Inf Diseases 2007) and investigated short and longer term response rates to a large series of vaccines given post therapy (starting at 6 months post therapy completion). They showed that a single booster vaccination for each vaccine improved immunity to those diseases and enabled protective levels to well over 90% overall. The UK has therefore adopted this as their standard approach for many years and this is the model we have recently changed to in BC. In addition, we are currently involved in a Cross-Canadian research study that is looking at this approach in BC, and are including some of the newer vaccines (pneumococcal and meningococcal) in survivors of childhood ALL. We are excited that this study will add to the very limited studies done thus far in this important area of research.

Vaccination in Special Populations

There are two main groups of children who need special consideration when it comes

to vaccinations: the stem cell transplant population and children who have reduced splenic function. The spleen plays a crucial role in protecting us from encapsulated bacteria, and overwhelming sepsis causing injury or death is unfortunately common in those who have reduced splenic function. This group of patients therefore need extra vaccines to ensure protection from meningococcus and pneumococcus. Those who have had spleens removed are easy to identify, but the group to take note of are those who have splenic dysfunction from treatment, including those whose spleens were in the radiation field (total body irradiation, abdominal radiation for Wilms/Hodgkins/Neuroblastoma) and those with chronic graft versus host disease. The stem cell transplant group are also high risk for infection and need extra vaccinations. However, the timing for starting vaccination in this group is later due to the need to wait immune reconstitution.

New Vaccination Clinic at BCCH

A new vaccination clinic has just opened on site. Located in the Ambulatory Care Building and open weekdays from 8:30am to 5pm, this clinic will offer all publically funded vaccines for free (including the yearly flu shot) for patients and their families. We are working with Dr Sadarangani (medical lead of the clinic) to determine a process for streamlining our survivors of childhood cancer to receive their vaccines during their follow-up visits. We hope that once this process is finalized the rates of vaccination in our childhood cancer survivors will improve and that we will offer the best level of protection for our children.

Oncology Hematology BMT inpatient and outpatient have moved. We are now located on level 8 of the Teck Acute Care Centre (TACC) at entrance # 53.

All contact information remains the same:

Inpatient telephone: 604-875-2345 extension 7614.

Outpatient phone: 604-875-2116.

Flu vaccine guidelines for 2017-18 are now available on the website.
<http://www.bcchildrens.ca/health-professionals/clinical-resources/oncology>



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 health care 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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