Ac²orn ADVOCACY FOR CANADIAN CHILDHOOD ONCOLOGY RESEARCH NETWORK

Canadian Childhood, Adolescent and Young Adult Cancer Statistics and Facts

Prevalence

Approximately **3,800 children, adolescents and young adults are diagnosed with cancer each year in Canada** (between the ages of 0-29 years).[1]

Approximately **1,500 children and adolescents were diagnosed with cancer in Canada in 2017** (between the ages of 0-19 years).[2]

Cancer causes the **greatest number of childhood deaths** of any disease.[3]

Cancer **is the second most common cause of death for children** in the developed world, second only to accidental death.[4]

Cancer incidence rates are slightly higher in boys than girls.[5]

Childhood cancer **incidence rates are slowly increasing over time**.[6]

There is very little known about the causes of childhood cancer.[7]

In Canada, childhood cancer accounts for less than 1% of all newly diagnosed cases of cancer (for ages 0-19 years).[8,9]

In Canada, cancer among adolescents and young adults ages 15-29 account for 1.5% of all newly diagnosed cancers.[10]

A rare disease is a condition impacting less than 1 person in 2000 in their lifetime.[11] Childhood, adolescent and young adult cancer is considered a rare disease. **The smaller patient population allows for nimble and targeted research, fosters international scientific collaboration, and facilitates the ability to pilot system change in a high-need patient group to understand if there is benefit to the entire health system.**

Survival and Mortality

Approximately **416 Canadian children, adolescents and young adults die from their cancer every year** (between the ages of 0-29 years).[12]

Approximately **1 child dies every day from cancer in Canada** (between the ages of 0-29 years).

The **five-year survival rate for Canadian children with cancer has improved from 71% to 82%** (late 1980s to the early 2000s).[13] This increase is directly attributable to clinical trials.[14]

Between 1968 and 1993, almost 13,000 children with acute lymphoblastic leukaemia (ALL) were treated on clinical trials and survival improved from less than 10% to over 70%.[15]

If pediatric cancer is not treated, and not treated properly, it is a disease which is almost uniformly fatal.

Brain/CNS cancer (34%), leukemia (26%) and neuroblastoma (11%) are the three cancers that account for the majority of deaths in children aged 0-14 years old in Canada.[16]

Leukemia (17%), brain/cns cancer (15%), and bone cancers (11%) are the three cancers that account for the majority of deaths in adolescents and young adults aged 15-29 years old in Canada. [17]

Adolescents and Young Adults (15-29 years of age)

The most common cancers for adolescents and young adults are thyroid cancer (17%), testicular cancer (14%), Hodgkin lymphoma (11%), and melanoma (7%).[18]

In this transitional age group, cancer can have characteristics that are either common in childhood cancer or that are common in adult cancers.

Advancements in treatment and overall survival for AYA with cancer has been extremely limited over recent years.[19,20]

Treatment and Drugs

In the USA and since 1980, only four drugs have been developed and approved for the primary use in pediatric, adolescent and some young adult cancers:

1. Teniposide (Vumon), approved in 1980 for ALL.
2. Clofarabine (Clolar), approved in 2004 for ALL.
3. Dinutuximab (Unituxin, ch14.18), approved in 2015 for neuroblastoma
4. Tisagenlecleucel (Kymriah, CAR T-Cell), approved in 2017 for ALL (pediatric and adult).

In Canada and since 1984, **only two drugs have been approved for the primary use in pediatric, adolescent and some young adult cancers**. These are Vumon and Clolar.

The survival rates for many pediatric cancers have stalled. This is true for acute myeloid leukaemia, many brain tumours, bone tumours, neuroblastoma, and sarcomas such as rhabdomyosarcoma with unacceptably low 5 year survival rates.[21]

Long-Term Effects of Treatment

Approximately **40% of childhood cancer survivors will experience late-effects from their treatment that are classified as life-threatening, disabling, and even fatal** at 30 years post diagnosis.[22]

By age 45, 80% of survivors have a life-threatening health condition – directly resulting from harsh treatment with chemotherapy and radiation.[23]

Children who undergo hematopoetic stem cell transplantation as part of their treatment experience an even greater degree of late-effects in comparison to those children treated with more conventional therapies.[24]

Long-term treatment related complications include auditory impairment, impaired cognition, psychosocial effects, cataracts, dental abnormalities, heart disease and failure, lung damage, liver dysfunction, kidney dysfunction, bladder complications, thyroid dysfunction, puberty complications, infertility, growth deficiency, scoliosis, bone density issues, and secondary malignancies.[25]

Long-term effects can show up shortly after treatment or years later. **There is also no plateau for these late-effects, with a high possibility that issues will become worse over time**.

A great number of studies have reported on the additional effects of pediatric cancer resulting in issues with employment status, the holding of lower-skilled jobs,[26], the inability to live an independent life,[27] have successful long-term relationships and other socio-economic indicators.

With childhood cancer treatment now resulting in the survival of over 80% of patients, there is an increasing **need for the long-term follow up of late effects throughout the entire lifetime** of these children.[28]

"Childhood cancer is still rare, but the number of years survivors potentially have ahead of them means their impact on the economy and society is equivalent to that of the much more numerous breast-cancer survivors, said David Malkin, medical director of the Pediatric Oncology Group of Ontario (POGO). While 60-65% of child patients survived cancer a generation ago, the rate is now 80-85%, he said."[29]

Children are NOT Little Adults

Cancers in children are typically a result of **changes in the DNA**; however, adult cancers are often due to environmental factors (i.e., exposure to carcinogens), lifestyle choices (i.e., obesity, smoking), and cellular aging. Unlike adults, children cannot make life choices which will help reduce their chances of a cancer diagnosis.

Children have **different physiology** than adults. How a child's body deals with medication (pharmacokinetics) and how medications affect the child's body (pharmacodynamics) is very different to what occurs in adults. As a child grows and develops, from infant to child to adolescent to teen, a medication can impact them differently at various stages of their development.

The **disease behaves differently** in children, is often more aggressive and frequently metastasizes to other parts of the body. Excluding systematic cancers such as leukemia, approximately 25%[30] of children diagnosed with cancer present with metastatic disease. This is significantly higher for certain types of childhood cancers (e.g., in stage IV neuroblastoma, approximately 75% of children present with metastatic disease). This is not to the same degree as adult cancers, with adult cancers often being more indolent in their presentation and course.

Cancers such as leukemia, lymphoma, neuroblastoma, and retinoblastoma mainly affect children and are **rarely diagnosed in adults**. Even though children and adults might be diagnosed with a cancer that is called by the same name, these "are frequently different on both phenotypic and molecular levels".[31]

Childhood cancers **frequently respond to treatments** such as chemotherapy and children are often able to tolerate the treatments better than adults. Interestingly, the maximum tolerated dose (MTD) of a drug for children is often not much lower than the MTD of the same drug for adults.[32] Children typically do not have additional co-morbidities that may cause added challenges to therapy (i.e., obesity).

Clinical Trials in Canada

Approximately 90% of children who are diagnosed with cancer are cared for at a Children's Oncology Group (COG) institution. They focus exclusively on the development of new treatments and ultimately cures for childhood cancer which is predominantly accomplished through the machinery of clinical trials.[33]

Approximately 26% of children and adolescents (ages 0-14 years) are enrolled on a clinical trial at the time of diagnosis.[34]

Approximately 44% of children and adolescents (ages 0-14 years) follow a clinical trial protocol but are not registered on a clinical trial at the time of diagnosis.[35] Often, if a clinical trial is not available at the time of diagnosis, patients will often follow the most successful phase 3 protocol but not be formally registered on the clinical trial.

Approximately 70% of children and adolescents (ages 0-14 years) are enrolled on a clinical trial or follow a clinical trial protocol at the time of diagnosis.[36] To compare, less than 4.5% of adults with cancer enroll on clinical trials in Canada.[37]

Approximately **25-27% of patients between the ages of 0-14 are enrolled on a therapeutic clinical trial** for their initial cancer diagnosis.[38]

Children with cancer **enrolled on clinical trials tend to do better** than those children who are treated with standard of care but not on clinical trials (also called an "inclusion benefit").[39,40,41,42]

This **"inclusion benefit"**[43,44] applies to children enrolled on any treatment arm of a clinical trial (control and intervention arms) versus those children who are not enrolled on a clinical trial. In the adult cancer world, this "inclusion benefit" also holds true.[45,46]

Children **fair better when treated at a COG affiliated hospital** and this is especially true for adolescents and young adults with cancer.[47]

Overall, children receiving care at **hospitals that run clinical trials have better outcomes**.[48]

There are many reasons why a patient might not enroll on a clinical trial. These include:[49]

1. A clinical trial did not exist for the patient's disease type at the time of need.
2. A clinical trial was in the process of being approved by its research ethics board and had not been approved/opened when the patient needed the clinical trial.
3. The patient's treating institution did not activate an available clinical trial.
4. The patient did not meet the clinical trial's eligibility criteria.
5. The patient enrolled on the clinical trial but was unable to continue on the trial due to various reasons (e.g., unable to harvest the necessary amount of stem cells, the disease progressed)
6. The patient was not offered an open clinical trial by their treating physician.
7. The patient declined the clinical trial and/or further treatment.

The most common reason for not enrolling on a clinical trial at the time of diagnosis is that a clinical trial is not available. This is true for 68% of Canadian patients.[50]

The **least common reason for not enrolling on a clinical trial is refusal by the patient/family**.[51]

Canada and the Pharmaceutical Industry

In Canada, pharmaceutical companies who develop pediatric drugs are granted a data protection extension allowing the company to have market exclusivity for an additional six month before generic versions of the drug can be approved for sale in the country (on top of the 8 years that are awarded for innovative drugs).

"Manufacturers are neither required to generate nor provide data on drug safety and efficacy in children, and Health Canada can request, but not compel, a manufacturer to submit results of any such studies."[52]

In the USA, the Creating Hope Act was passed in 2012 to establish a pediatric priority review voucher program to incentivize pharmaceutical companies to develop drugs specifically for children with cancer and other rare diseases. In 2017, the RACE for Children Act was passed that requires companies developing targeted cancer therapies for adults, to also develop these therapies for children.[53] These types of legislation do not currently exist in Canada.

Scientific Contributions

An abridged history of the scientific contributions that childhood, adolescent and young adult cancer research has realized over the last 50 years:

- 1940s: Sydney Farber discovered the effectiveness of achieving remissions in children with leukemia using folic acid antagonists. Children were the first patients to demonstrate the positive impact of chemotherapy on treating cancer.
- 1950s-1960s: The first combination chemotherapy regimens were used to treat leukemia.
- 1960s-1979s: Study V and follow-up clinical trials developed an aggressive protocol to treat childhood leukemia which resulted in survival rates of almost 70%.[54]
- 1967: Achievement of significant remissions in patients with non-metastatic Wilms' Tumour using Actinomycin-D, surgery and radiation.
- 1969: Improved treatment of Wilm's Tumour based on disease staging and reducing the duration of chemotherapy for lower staged disease.
- 1970s/1980s: The use of multi-agent chemotherapies for Ewing's Sarcoma discovered a decrease in relapse rates.
- 1986/7: The first tumour suppressor gene, RB1, was identified and this genetic alteration was proven to be the cause of a childhood cancer called retinoblastoma.[55]
- 1988: Established staging system for neuroblastoma and the importance of understanding MYCN amplification.
- 2004: The FDA approves the drug clofarabine (Colar, owned by Senofi) for the treatment of refractory pediatric ALL. The drug was approved without having prior approval as an adult oncology intervention.[56]
- 2012: The first pediatric patient with relapsed ALL is treated with modified CAR T-cell therapy at the Children's Hospital of Philadelphia.

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