Cancer Association of South Africa (CANSA)

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Fact Sheet on Childhood Chronic Lymphoblastic Leukaemia (CLL)

Introduction

Leukaemia is a cancer that starts in early blood-forming cells. Most often, leukaemia is a cancer of the white blood cells, but some leukaemias start in other blood cell types.

Any of the cells from the bone marrow can turn into a leukaemia cell. Once this change takes place, the leukaemia cells do not go through the normal process of maturing. Leukaemia cells might reproduce quickly, and not die when they should. They survive and build up in the bone marrow, crowding out normal cells. In most cases the leukaemia cells spill into the bloodstream fairly quickly. From there it can go to other parts of the body such as the lymph nodes, spleen, liver, central nervous system (the brain and spinal cord), testicles, or other organs, where they can keep other cells in the body from functioning normally.

[Picture Credit: Chronic Lymphoblastic Leukaemia]

Some other childhood cancers, such as neuroblastoma or Wilms tumour, start in other organs and can spread to bone marrow, but these cancers are not leukaemia.

Auger, N., Goudie, C., Low, N., Healy-Profitós, J., Lo, E. & Luu, T.M. 2019.
BACKGROUND: Previous studies provide conflicting evidence of a link between maternal substance use and risk of childhood cancer.
METHODS: We analyzed a cohort of 785,438 newborns in Quebec (2006-2016). We identified infants whose mothers had problematic illicit drug, tobacco, or alcohol use before or during pregnancy. The primary outcomes were childhood hematopoietic cancer or solid tumors within 0-5 years of age. Using Cox proportional hazards models, we computed hazard ratios (HR) and 95% confidence intervals (CI) for the association between maternal substance use and childhood cancer, adjusted for potential confounders.
RESULTS: A total of 925 cases of cancer occurred during 3.5 million person-years of follow-up. Children exposed to any maternal substance use had marginally elevated cancer incidence rates compared with unexposed children (29.4 vs. 26.1 per 100,000 person-years). Maternal illicit drug use was associated with the risk of acute lymphoblastic leukemia (HR 1.63, 95% CI 0.79-3.36)

and fibrosarcoma (HR 2.11, 95% CI 0.86-5.16). Maternal tobacco use was associated with acute myeloid leukemia (HR 2.01, 95% CI 0.72-5.60) and fibrosarcoma (HR 2.13, 95% CI 1.05-4.32), but a weak association with neuroblastoma (HR 1.21, 95% CI 0.61-2.40) and renal tumors (HR 1.14, 95% CI 0.42-3.13) also appeared to be present.
CONCLUSIONS: We found a potential association between maternal substance use and certain types of early childhood cancer. Although effects were modest, maternal substance use may contribute to some types of childhood cancer, especially leukemia and fibrosarcoma.

Childhood Chronic Lymphoblastic Leukaemia (CVLL)
Although leukaemia is the most common type of childhood cancer, leukaemia in children is nearly always acute leukaemia – either acute myeloid Leukaemia or Acute Lymphoblastic Leukaemia. Chronic leukaemia is very rare in children.

It is much more common to get Chronic Lymphoblastic Leukaemia (CLL) if one is older. It is more common in people over the age of 60 and is very rare in individuals under 40. Men are more likely to develop CLL than women. The reasons for this are unclear (Demir, *et al*, 2014).

Chronic lymphoblastic leukaemia (also called CLL) is a blood and bone marrow disease that usually gets worse slowly. CLL is the second most common type of leukaemia in adults. It often occurs during or after middle age; it, however, rarely occurs in children.
A myeloid stem cell becomes one of three types of mature blood cells:

- Red blood cells that carry oxygen and other substances to all tissues of the body
- White blood cells that fight infection and disease
- Platelets that form blood clots to stop bleeding

A lymphoid stem cell becomes a lymphoblast cell and then one of three types of lymphocytes (white blood cells):

- B lymphocytes that make antibodies to help fight infection
- T lymphocytes that help B lymphocytes make antibodies to fight infection
- Natural killer cells that attack cancer cells and viruses

In CLL, too many blood stem cells become abnormal lymphocytes and do not become healthy white blood cells. The abnormal lymphocytes may also be called leukaemia cells. The lymphocytes are not able to fight infection very well. Also, as the number of lymphocytes increases in the blood and bone marrow, there is less room for healthy white blood cells, red blood cells, and platelets. This may cause infection, anaemia, and easy bleeding.

Dixon, S.B., Chen, Y., Yasui, Y., Pui, C.H., Hunger, S.P., Silverman, L.B., Ness, K.K., Green, D.M., Howell, R.M., Leisenring, W.M., Kadan-Lottick, N.S., Krull, K.R., Oeffinger, K.C., Neglia, J.P., Mertens, A.C., Hudson, M.M. & Robison, L.L. 2020.
Purpose: Risk-stratified therapy, which modifies treatment on the basis of clinical and biologic features, has improved 5-year overall survival of childhood acute lymphoblastic leukemia (ALL) to 90%, but its impact on long-term toxicity remains unknown.
Methods: We assessed all-cause and health-related late mortality (including late effects of cancer therapy), subsequent malignant neoplasms (SMNs), chronic health conditions, and neurocognitive outcomes among 6,148 survivors of childhood ALL (median age, 27.9 years; range, 5.9-61.9 years)

diagnosed between 1970 and 1999. Therapy combinations and treatment intensity defined 6 groups: 1970s-like (70s), standard- or high-risk 1980s-like (80sSR, 80sHR) and 1990s-like (90sSR, 90sHR), and relapse/transplantation (R/BMT). Cumulative incidence, standardized mortality ratios, and standardized incidence ratios were compared between treatment groups and with the US population.
Results: Overall, 20-year all-cause late mortality was 6.6% (95% CI, 6.0 to 7.1). Compared with 70s, 90sSR and 90sHR experienced lower health-related late mortality (rate ratio [95% CI]: 90sSR, 0.2 [0.1 to 0.4]; 90sHR, 0.3 [0.1 to 0.7]), comparable to the US population (standardized mortality ratio [95% CI]: 90sSR, 1.3 [0.8 to 2.0]; 90sHR, 1.7 [0.7 to 3.5]). Compared with 70s, 90sSR had a lower rate of SMN (rate ratio [95% CI], 0.3 [0.1 to 0.6]) that was not different from that of the US population (standardized incidence ratio [95% CI], 1.0 [0.6 to 1.6]). The 90sSR group had fewer severe chronic health conditions than the 70s (20-year cumulative incidence [95% CI], 11.0% [9.7% to 12.3%] *v* 22.5% [19.4% to 25.5%]) and a lower prevalence of impaired memory (prevalence ratio [95% CI], 0.7 [0.6 to 0.9]) and task efficiency (0.5 [0.4 to 0.7]).
Conclusion: Risk-stratified therapy has reduced late morbidity and mortality among contemporary survivors of standard-risk ALL, represented by 90sSR. Health-related late mortality and SMN risks among 5-year survivors of contemporary, standard-risk childhood ALL are comparable to the general population.

Allegra, A., Musolino, C., Tonacci, A., Pioggia, G., Casciaro, M. & Gangemi, S. 2020.
"B-cell chronic lymphocytic leukemia (B-CLL) is the main cause of mortality among hematologic diseases in Western nations. B-CLL is correlated with an intense alteration of the immune system. The altered functions of innate immune elements and adaptive immune factors are interconnected in B-CLL and are decisive for its onset, evolution, and therapeutic response. Modifications in the cytokine balance could support the growth of the leukemic clone via a modulation of cellular proliferation and apoptosis, as some cytokines have been reported to be able to affect the life of B-CLL cells in vivo."

Incidence of Childhood Chronic Lymphoblastic Leukaemia (CLL)
In providing the incidence figures of leukaemia in South Africa, The National Cancer Registry (2017) does not make provision for the reporting of the different types of leukaemia – it also does not differentiate between acute and chronic leukaemia.

According to the National Cancer Registry (2017) the following number of leukaemia cases was histologically diagnosed in South Africa during 2017. Histologically diagnosed means that a sample of tissue (blood, in this case) was forwarded to an approved laboratory where a specially trained pathologist confirmed the diagnosis of Leukaemia.

Group – Boys 0 to 19 Years 2017	Actual No of Cases
All boys	82
Asian boys	0
Black boys	66
Coloured boys	7
White boys	9

Group – Girls 0 to 19 Years 2017	Actual No of Cases
All girls	40
Asian girls	1
Black girls	32
Coloured girls	1
White girls	6

The frequency of histologically diagnosed cases of leukaemia in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Boys 2017	0 – 4 Years	5 – 9 Years	10 – 14 Years	15 – 19 Years
All boys	19	25	24	14
Asian boys	0	0	0	0
Black boys	16	20	21	9
Coloured boys	0	5	1	2
White boys	3	1	3	3

Group - Girls 2017	0 – 4 Years	5 – 9 Years	10 – 14 Years	15 – 19 Years
All girls	11	17	5	10
Asian girls	0	0	0	1
Black girls	7	15	4	6
Coloured girls	1	0	0	0
White girls	3	2	1	0

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all boys' and 'all girls', however, always reflect the correct totals.

Signs and Symptoms of Childhood Chronic Lymphoblastic Leukaemia (CLL)

Usually CLL does not cause any symptoms and is found during a routine blood test. Sometimes symptoms occur that may be caused by CLL or by other conditions. A doctor should be consulted if any of the following problems are present over an extended period:

- Painless swelling of the lymph nodes in the neck, underarm, stomach, or groin
- Feeling very tired
- Fatigue
- Pain or fullness below the ribs
- Pain in the upper left portion of the abdomen, which may be caused by an enlarged spleen
- Fever and infection
- Night Sweats
- Weight loss for no known reason
- Bruising or bleeding easily
- Frequent infections

Diagnosis of Childhood Chronic Lymphocytic Leukaemia
The following tests and procedures may be used:

Physical examination and history: An examination of the body to check general signs of health, including checking for signs of disease, such as lumps or anything else that seems unusual. A history of the patient's health habits and past illnesses and treatments will also be taken.

Complete blood count (CBC) with differential. Blood is collected by inserting a needle into a vein and allowing the blood to flow into a tube. The blood sample is sent to the laboratory and the red blood cells, white blood cells, and platelets are counted. The CBC is used to test for, diagnose, and monitor many different conditions.

Immunophenotyping - a laboratory test in which the antigens or markers on the surface of a blood or bone marrow cell are checked to see if they are lymphocytes or myeloid cells. If the cells are malignant lymphocytes (cancer), they are checked to see if they are B lymphocytes or T lymphocytes.

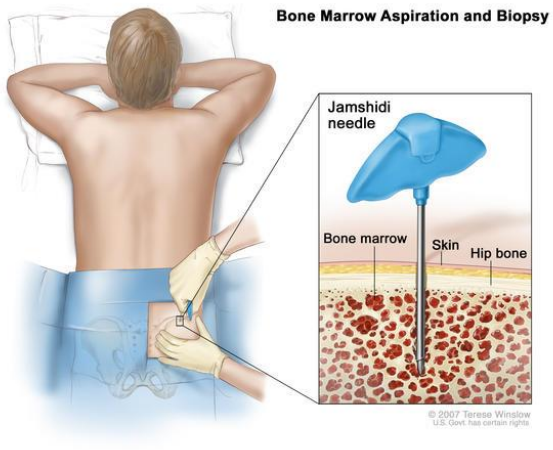
FISH (fluorescence *in situ* hybridisation) - a laboratory technique used to look at genes or chromosomes in cells and tissues. Pieces of DNA that contain a fluorescent dye are made in the laboratory and added to cells or tissues on a glass slide. When these pieces of DNA bind to specific genes or areas of chromosomes on the slide, they light up when viewed under a microscope with a special light.

Flow cytometry - a laboratory test that measures the number of cells in a sample, the percentage of live cells in a sample, and certain characteristics of cells, such as size, shape, and the presence of tumour markers on the cell surface. The cells are stained with a light-sensitive dye, placed in a fluid, and passed in a stream before a laser or other type of light.

[Picture Credit: Flow Cytometry]

The measurements are based on how the light-sensitive dye reacts to the light.

IgVH gene mutation test - a laboratory test done on a bone marrow or blood sample to check for an *IgVH* gene mutation. Patients with an *IgVH* gene mutation have a better prognosis. Bone marrow aspiration and biopsy: The removal of bone marrow, blood, and a small piece of bone by inserting a hollow needle into the hipbone or breastbone. A pathologist views the bone marrow, blood, and bone under a microscope to look for abnormal cells.



[Picture Credit: Bone Marrow Aspiration]

Bone marrow aspiration and biopsy. After a small area of skin is numbed, a Jamshidi needle (a long, hollow needle) is inserted into the patient's hip bone. Samples of blood, bone, and bone marrow are removed for examination under a microscope

Treatment of Childhood Chronic Lymphoblastic Leukaemia

Treatment options depend on:

- The stage of the disease.
- Result of the complete blood count
- Presence of any signs or symptoms, such as fever, chills, or weight loss.
- Presence of enlarged liver, spleen, or lymph nodes are larger than normal.
- Whether the CLL has recurred (come back).
- The patient's general health.

Treatment usually comprises:

- standard treatment usually used:
    - Watchful waiting
    - Radiation therapy
    - Chemotherapy
    - Surgery
    - Targeted therapy
- New types of treatment that are being tested in clinical trials.
    - Chemotherapy with stem cell transplant
    - Biologic therapy
    - Chimeric antigen receptor (CAR) T-cell therapy

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa.

The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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