Cancer Association of South Africa (CANSA)

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Fact Sheet on Childhood Acute Lymphoblastic Leukaemia (ALL)

Introduction

Leukaemia is a type of blood cancer. The word *leukaemia* literally means 'white blood' and is used to describe a variety of cancers that begin in the blood-forming cells (lymphocytes) of the bone marrow.

[Picture Credit: Childhood Leukaemia]

Leukaemias are divided into two major types:

- Acute Leukaemia which often progresses rapidly if not treated
- Chronic Leukaemia which usually progresses more slowly

Childhood acute lymphoblastic leukaemia (ALL) is a type of blood cancer that affects the bone marrow, white blood cells, red blood cells, and blood platelets. In the case of ALL too many immature white blood cells (lymphocytes) are manufactured.

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

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Reviewed by
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

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.

Incidence of Childhood Acute Lymphoblastic Leukaemia (ALL)
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.

Kakaje, A., Alhalabi, M.M., Ghareeb, A., Karam, B., Mansour, B., Zahra, B., Hamdan, O. 2020.
"Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer and has a high survival rate when properly managed. Prognosis is correlated with many factors such as age, gender, white blood cell (WBC) count, CD10, French-American-British (FAB) classification, and many others. Many of these factors are included in this study as they play a major role in establishing the best treatment protocol. This study aims to demonstrate clinical and laboratory features of childhood ALL in Syria. They were treated at Children's University Hospital, the only working major cancer centre in Syria at the time of the study. Data of 203 patients who aged 0-14 years were obtained for this study. Most patients (48.8%) aged (5-9) years with a male predominance (60.9%). The major features for ALL included lymphadenopathy (82.9%), presenting with systemic symptoms (74.9%), T-ALL subclass (20.2%), L2 FAB classification (36.1%), low educational levels for fathers (53%) and mothers (56.2%), having a high risk (48.4%), and having a duration of symptoms before evaluation for more than 4 weeks (42.6%). Only three (1.5%) patients had normal full blood counts (FBC) and only one (0.5%) patient had an isolated high WBC count at time of presentation. Most patients had either abnormal platelet count (89.3%) or low haemoglobin level (88.8%) when presenting with only (2.0%) having normal levels for both. This suggests that having normal haemoglobin and platelet count can be used for quick screening in crisis time like in Syria for prioritising patients. Many prognostic factors were significantly different from medical literature which emphasises the importance of local studies in the developping countries. This study included a high prevalence of T-all, L2 FAB classification, high-risk and other variables which require further studies to evaluate the aetiology of these features, especially that treatment protocols may have a higher mortality in developing countries when not adjusted to local variables."

Childhood Acute Lymphoblastic Leukaemia (ALL)
Leukaemia is the most common childhood cancer worldwide with acute lymphoblastic leukaemia (ALL), an aggressive (fast growing) leukaemia contributing to 76% of all leukaemia cases (PubMed Health Glossary). Hossain, Xie, & McCahan, 2014 states that: "ALL is a malignant blood disorder that originates either from the T- or B-cell lineage, and it is hallmarked by subtype heterogeneity in chromosomal abnormalities, immunophenotypes, and treatment responsiveness."

Stanulla, M., CAvé, H. & Moorman, A.V. 2020.
"Improved personalized adjustment of primary therapy to the perceived risk of relapse by using new prognostic markers for treatment stratification may be beneficial to patients with acute lymphoblastic leukemia (ALL). Here, we review the advances that have shed light on the role of IKZF1 aberration as prognostic factor in pediatric ALL and summarize emerging concepts in this field. Continued research on the interplay of disease biology with exposure and response to treatment will be key to further improve treatment strategies."

Possible Triggers, Causes and Risks of Childhood Acute Lymphoblastic Leukaemia

"In children, the most common cancer is leukaemia, predominantly acute lymphoblastic leukaemia (ALL), although these diseases are relatively rare in childhood: depending on the country the incidence rates range from 1.5 to 5.0 per 100 000. Molecular studies have revealed a two-stage origin of many childhood leukaemias: a preleukaemic stem cell clone (*initiation* and *promotion*) is thought to be generated *in utero* and, in a minority of children, the progress to the full-blown disease takes place after birth when a number of postnatal genetic and epigenetic alterations have set in (*progression*); as in many other malignant neoplasms the nature of pre- and post-natal events involved in leukaemogenesis in children is not well understood." (Janiak, M.K., 2014). The above findings were also established by Belson, Kingsley, & Holmes (2007) during their research.

Some identified risk factors for childhood acute lymphoblastic leukaemia include:

Exposure to home paint fumes - home paint exposure shortly before conception, during pregnancy and/or after birth appears to increase the risk of childhood ALL. The researchers are of the opinion that it may be prudent to limit exposure to home paint fumes during these periods. Bailey, *et al*., 2011; Bailey, *et al*., 2015).

According to PubMed Health Glossary (no date), possible causes and risk factors for childhood acute lymphoblastic leukaemia (ALL) include:

- Having been exposed to X-rays before birth
- Previous chemotherapy treatment
- Exposure to radiation
- Genetic conditions:
    - Down syndrome
    - Bloom Syndrome
    - Li-Fraumeni Syndrome
    - Neurofibromatosis type 1
    - Ataxia-telengiectasia
    - Fanconi anaemia
- Mutations in certain genes that stop DNA from repaiding itself
- Having some changes in genes or chromosome

Signs and Symptoms of Childhood Acute Lymphoblastic Leukaemia (ALL)

Signs of childhood ALL include fever and bruising.

- Pyrexia (fever)
- Pale skin
- Easy bruising or episodes of bleeding
- Frequent infections
- Flat, pinpoint, dark-red spots under the skin (petechiae)
- Bone or joint pain
- Lumps: underarm, in the neck, groin or abdomen
- Tiredness
- Loss of appetite

- General decrease in energy

(PubMed Health Glossary, no date).

Diagnosis of Childhood Acute Lymphoblastic Leukaemia

The following may be used in diagnosis:

- Taking of a complete medical history
- Full physical examination
- Blood chemistry comprising a full blood count with differential cell count
- Chest X-ray
- Bone marrow aspiration and biopsy
- Laboratory test in which the cells in a sample of blood or bone marrow are viewed under a microscope to look for certain changes in the chromosomes in the lymphocytes, e.g. whether it is Philadelphia chromosome-positive

Treatment of Childhood Acute Lymphoblastic Leukaemia

The aim of treatment for ALL is to destroy the leukaemia cells and enable the bone marrow to work normally again. Chemotherapy is the main treatment for ALL. The treatment is given in several phases, namely:

- Induction
- Consolidation
- After this consolidation treatment there is a recovery period which is called interim maintenance.
- Possibly further doses of chemotherapy treatment, called delayed intensification, Maintenance treatment
- Bone marrow transplantation (only used for children with ALL that is likely to come back)
- Possible testicular radiotherapy (in some situations because leukaemia cells can survive in the testicles despite chemotherapy)

Kloos, R.Q.H., Pieters, R., Jumelet, F.M.V., de Groot-Kruseman, H.A., van den Bos, C. & van der Sluis, I.M. 2020.

Purpose: In the DCOG ALL-11 protocol, polyethylene glycol-conjugated *Escherichia coli* asparaginase (PEGasparaginase) and *Erwinia* asparaginase treatment of pediatric acute lymphoblastic leukemia are individualized with therapeutic drug monitoring (TDM). The efficacy of TDM and its effect on asparaginase-associated toxicity are reported.

Patients and methods: After induction with 3 fixed intravenous doses of 1,500 IU/m^2 PEGasparaginase, medium-risk patients (n = 243) received 14 individualized doses that targeted trough levels of 100-250 IU/L, standard-risk patients (n = 108) received 1 individualized dose, and high-risk patients (n = 18) received 2-5 fixed administrations (1,500 IU/m^2). After a neutralizing hypersensitivity reaction, patients were started with 20,000 IU/m^2 *Erwinia* asparaginase 3 times per week, and l-asparagine was measured to monitor asparaginase efficacy. Several asparaginase-associated toxicities were studied.

Results: The final median PEGasparaginase dose was lowered to 450 IU/m^2. Overall, 97% of all trough levels of nonallergic patients were > 100 IU/L. Asparagine was < 0.5 µM in 96% and 67% of the PEGasparaginase and *Erwinia* asparaginase levels > 100 IU/L, respectively. Ten percent developed a neutralizing hypersensitivity reaction to PEGasparaginase, of which 40% were silent inactivations. The cumulative incidence of grade 3-4 pancreatitis, central neurotoxicity, and thromboses was 12%, 4%, and 6%, respectively, and not associated with asparaginase activity levels. During medium-risk intensification, 50% had increased ALT and 3% hyperbilirubinemia (both grade 3/4 and correlated with asparaginase activity levels), and 37% had grade 3/4 hypertriglyceridemia. Hypertriglyceridemia occurred less in intensification compared with ALL-10 (37% *v* 47%), which is similar to ALL-11 but with higher asparaginase levels during intensification.
Conclusion: TDM of asparaginase results in a significant reduction of the PEGasparaginase dose with adequate asparaginase activity levels and sufficient asparagine depletion. In addition, with TDM, silent inactivation and allergic-like reactions were identified. However, the effect of reduced asparaginase activity levels on toxicity is limited.

Malard, F. & Mohty, M. 2020
"Acute lymphoblastic leukaemia develops in both children and adults, with a peak incidence between 1 year and 4 years. Most acute lymphoblastic leukaemia arises in healthy individuals, and predisposing factors such as inherited genetic susceptibility or environmental exposure have been identified in only a few patients. It is characterised by chromosomal abnormalities and genetic alterations involved in differentiation and proliferation of lymphoid precursor cells. Along with response to treatment, these abnormalities are important prognostic factors. Disease-risk stratification and the development of intensified chemotherapy protocols substantially improves the outcome of patients with acute lymphoblastic leukaemia, particularly in children (1-14 years), but also in adolescents and young adults (15-39 years). However, the outcome of older adults (≥40 years) and patients with relapsed or refractory acute lymphoblastic leukaemia remains poor. New immunotherapeutic strategies, such as monoclonal antibodies and chimeric antigen receptor (CAR) T cells, are being developed and over the next few years could change the options for acute lymphoblastic leukaemia treatment."

Rafei, H., Kantarjian,H.M. & Jabbour, E. 2019.
"Acute lymphoblastic leukemia (ALL) is a heterogeneous disease with a bimodal distribution. The progresses made in understanding its biology led to the development of targeted therapies. In this review, we summarize the current and future approaches in management of adult ALL. Tyrosine kinase inhibitors (TKI) targeting BCR-ABL1 tyrosine kinase, monoclonal antibodies targeting cell surface antigens (CD19, CD20, and CD22), bispecific antibodies, and chimeric antigen receptor (CAR)-T therapy are breakthrough treatments. They resulted in FDA approvals of blinatumomab in 2014, inotuzumab ozagamicin in 2017, and tisagenlecleucel in 2017 for relapsed/refractory ALL. Currently, long-term survival is achieved in more than 50% of patients with precursor B-ALL (50-70% in patients with Philadelphia chromosome (Ph)-positive ALL), 50-60% T-ALL, and 80% mature B-ALL. Ongoing efforts exist to optimize therapeutic options in both the relapsed/refractory as well as the frontline settings. In the era of precision medicine, the future lies in using less cytotoxic and more targeted agents."

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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