Cancer Association of South Africa (CANSA)

Fact Sheet on Juvenile Myelomonocytic Leukaemia (JMML)

Introduction
The term leukaemia refers to cancers of the white blood cells (also called leukocytes or WBCs). When someone has leukaemia, large numbers of abnormal white blood cells are produced in the bone marrow. These abnormal white cells crowd the bone marrow and flood the bloodstream, but they cannot perform their proper role of protecting the body against disease because they are defective.

[Picture Credit: Blood Cell Formation I]

As leukaemia progresses, the cancer interferes with the body’s production of other types of blood cells, including red blood cells and platelets. This results in anaemia (low numbers of red blood cells) and bleeding problems, in addition to the increased risk of infection caused by white cell abnormalities.

Synonyms of Juvenile Myelomonocytic Leukemia

Synonyms include:
• chronic myelomonocytic leukaemia of infancy
• juvenile chronic myelogenous leukaemia (old literature)
**Juvenile Myelomonocytic Leukaemia (JMML)**

Juvenile Myelomonocytic Leukaemia is a rare childhood cancer that usually occurs in children younger than 2 years old. In JMML, too many myelocytes and monocytes (two types of white blood cells) are produced from immature blood stem cells called blasts. These, monocytes and blasts overwhelm the normal cells in the bone marrow and other organs, causing the symptoms of JMML.

**Niemeyer, C.M. & Flotho, C. 2019. Juvenile myelomonocytic leukemia: who’s the driver at the wheel?**

“Juvenile myelomonocytic leukemia (JMML) is a unique clonal hematopoietic disorder of early childhood. It is classified as an overlap myeloproliferative/myelodysplastic neoplasm by the World Health Organization (WHO) and shares some features with chronic myelomonocytic leukemia in adults. JMML pathobiology is characterized by constitutive activation of the Ras signal transduction pathway. About 90% of patients harbor molecular alterations in one of five genes (PTPN11, NRAS, KRAS, NF1 or CBL) which define genetically and clinically distinct subtypes. Three of these subtypes, PTPN11-, NRAS- and KRAS-mutated JMML, are characterized by heterozygous somatic gain-of-function mutations in non-syndromic children while two subtypes, JMML in neurofibromatosis type 1 and JMML in children with CBL-syndrome, are defined by germline Ras disease and acquired biallelic inactivation of the respective genes in hematopoietic cells. The clinical course of the disease varies widely and can in part be predicted by age, level of hemoglobin F and platelet count. The majority of children require allogeneic hematopoietic stem cell transplantation for long-term leukemia-free survival, but the disease will eventually resolve spontaneously in approximately 15% of patients, rendering the prospective identification of these cases a clinical necessity. Most recently, genome-wide DNA methylation profiles identified distinct methylation signatures correlating with clinical and genetic features and highly predictive for outcome. Understanding the genomic and epigenomic basis of JMML will not only greatly improve precise decision making, but also be fundamental for drug development and future collaborative trials.”

**Incidence of Juvenile Myelomonocytic Leukaemia (JMML)**

In providing the incidence figures of leukaemia in South Africa, The National Cancer Registry (2014) 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 (2014) the following number of leukaemia cases was histologically diagnosed in South Africa during 2014. 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.

<table>
<thead>
<tr>
<th>Group – Boys 0 to 19 Years 2014</th>
<th>Actual No of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>All boys</td>
<td>81</td>
</tr>
<tr>
<td>Asian boys</td>
<td>1</td>
</tr>
<tr>
<td>Black boys</td>
<td>49</td>
</tr>
<tr>
<td>Coloured boys</td>
<td>12</td>
</tr>
<tr>
<td>White boys</td>
<td>19</td>
</tr>
</tbody>
</table>
Group – Girls
0 to 19 Years
2014
<table>
<thead>
<tr>
<th></th>
<th>Actual No of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>All girls</td>
<td>54</td>
</tr>
<tr>
<td>Asian girls</td>
<td>2</td>
</tr>
<tr>
<td>Black girls</td>
<td>28</td>
</tr>
<tr>
<td>Coloured girls</td>
<td>10</td>
</tr>
<tr>
<td>White girls</td>
<td>12</td>
</tr>
</tbody>
</table>

The frequency of histologically diagnosed cases of leukaemia in South Africa for 2014 was as follows (National Cancer Registry, 2014):

<table>
<thead>
<tr>
<th></th>
<th>0 – 4 Years</th>
<th>5 – 9 Years</th>
<th>10 – 14 Years</th>
<th>15 – 19 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All boys</td>
<td>36</td>
<td>24</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Asian boys</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Black boys</td>
<td>20</td>
<td>18</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Coloured boys</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>White boys</td>
<td>7</td>
<td>4</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>0 – 4 Years</th>
<th>5 – 9 Years</th>
<th>10 – 14 Years</th>
<th>15 – 19 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All girls</td>
<td>28</td>
<td>13</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Asian girls</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Black girls</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Coloured girls</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>White girls</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

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.

Causes of Juvenile Myelomonocytic Leukaemia (JMML)
The cause of JMML is unknown, but doctors do know that certain medical conditions — such as neurofibromatosis type 1 and Noonan syndrome — can make a child more likely to develop it.

Signs and Symptoms of Juvenile Myelomonocytic Leukaemia (JMML)
Common symptoms for JMML include:
- Fever for no known reason
- Persistently feeling very tired and fatigued
- General weakness
- Shortness of breath
- Weight loss
- Easy bruising and/or bleeding
- Tendency to bleed from the nose and gums
- Recurring infections such as bronchitis or tonsillitis
- Sore mouth due to mouth ulcers
- Skin rash
- Painless swelling of lymph nodes in the neck, underarm, abdomen or groin
Pain of a feeling of fullness below the ribs

Diagnosis of Juvenile Myelomonocytic Leukaemia (JMML)
The first step in the diagnosis is a simple blood test called a full blood count (FBC) or complete blood count (CBC). This involves a sample of blood from a vein in your child’s arm being sent to the laboratory for investigation. Some children with JMML have elevated Haemoglobin F levels for their age.

If the results of the blood tests suggest JMML, a bone marrow biopsy may be required to help confirm the diagnosis. A bone marrow biopsy involves taking a sample of bone marrow (usually from the back of the hip bone) and sending it to the laboratory for examination under the microscope.

The sample of bone marrow is examined in the laboratory to determine the number and type of cells present and the amount of haematopoiesis (blood forming) activity taking place there. The diagnosis of JMML is confirmed by the presence of an excessive number of blast cells in the bone marrow.

Treatment of Juvenile Myelomonocytic Leukaemia (JMML)
Treatment options for JMML may include (alone or in combination):

- Chemotherapy
- Stem cell transplantation
- Biologic therapies that use the body’s immune system to fight the cancer
- Blood transfusions
- Antibiotics to prevent and treat infections

Sakashita, K., Matsuda, K. & Koike, K. 2016. "Juvenile myelomonocytic leukemia (JMML) is a rare myelodysplastic/myeloproliferative disorder that occurs during infancy and early childhood; this disorder is characterized by hypersensitivity of the myeloid progenitor cells to granulocyte-macrophage colony-stimulating factor in vitro. JMML usually involves somatic and/or germline mutations in the genes of the RAS pathway, including PTPN11, NRAS, KRAS, NF1, and CBL, in the leukemic cells. Almost all patients with JMML experience an aggressive clinical course, and hematopoietic stem cell transplantation (HSCT) is the only curative treatment. A certain proportion of patients with somatic NRAS and germline mutations in CBL, however, have spontaneous resolution. A suitable treatment after diagnosis and conditioning regimen prior to HSCT are yet to be determined, but several clinical trials have been initiated throughout the world to develop suitable pre- or post-allogeneic HSCT treatments and new targeted therapies that are less toxic, to improve patient outcome.”

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:

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]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]
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• 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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Sources and References Consulted or Utilised

Akron Children’s Hospital
https://www.akronchildrens.org/cms/kidshealth/b220bb746ad4e0e63/

Blood Cell Formation I
https://www.google.co.za/search?q=myelocytes+monocytes+in+blood&source=lnms&tbm=isch&sa=X&ei=cpxgU-evCIOKCPcmgDN&ved=0CAgQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=_&imgrc=97R-SNQLfrofTM%253A%3B5uaYIM_OYAfQMM%3Bhttp%253A%252F%252Fupload.wikimedia.org%252Fwikipedia%252Fcommons%252F2%252F20%252F1llu_blood_cell_lineage.jpg%3Bhttp%252F%252Fen.wikipedia.org%252Fwik%252FMegakaryocyte%3B480%3B350

Blood Cell Formation II
https://www.google.co.za/search?q=white+blood+cell+formation&source=lnms&tbm=isch&sa=X&ei=PaJgU7milc3XPL3xgK&ved=0CAgQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=_&imgrc=A9usLOO4lw5qQM%3B%3A%3BdP1mFfsKU4IbCM%3Bhttp%253A%252F%252Fdracula.univ-lyon1.fr%252Fimages%252Fhemato_1.jpg%3Bhttp%252F%252Fdracula.univ-lyon1.fr%252Fresearch.php%3B381053%3B745

Children’s Cancer Research Fund
http://www.childrenscancer.org/main/juvenile_myelomonocytic_leukemia_jmml/
Dana-Farber Boston Children’s Cancer and Blood Disorder Center

Kids Health

Leukaemia Foundation

National Cancer Institute
http://www.cancer.gov/cancertopics/pdq/treatment/mds-mdp/HealthProfessional/page3
http://www.cancer.gov/clinicaltrials/learningabout/what-are-clinical-trials
http://www.cancer.gov/about-cancer/treatment/clinical-trials
