Cancer Association of South Africa (CANSA)

Fact Sheet on Childhood Chronic Myeloid Leukaemia (CML)

Introduction
Childhood leukaemia, the most common type of cancer in children and teenagers, is a cancer of the white blood cells. Abnormal white blood cells form in the bone marrow. They quickly travel through the bloodstream and crowd out healthy cells. This increases the body's chances of infection and other problems.

As tough as it is for a child to have cancer, it's good to know that most children and teens with childhood leukaemia can be successfully treated.

Most childhood leukaemias are 'acute' meaning that they develop and progress rapidly.

Childhood Chronic Myeloid Leukaemia
Normally, WBCs help fight infection and protect the body against disease. But in leukaemia, WBCs turn cancerous and multiply when they shouldn't, resulting in too many abnormal WBCs, which then interfere with the body's ability to function normally.

If too many mature WBCs are made, a child will develop Chronic Myeloid Leukaemia (CML). While this type of leukaemia is more common in adults, it can affect children, too.

Thanks to advances in therapy and clinical trials, the outlook for kids with CML is promising. CML is caused by a chromosomal problem. The 23 pairs of chromosomes in the body each contain segments of DNA called genes. Genes are essentially the body's blueprints. CML occurs when a piece of chromosome 22 breaks off and switches places with a piece of chromosome 9. (This piece, containing parts of both chromosome 9 and chromosome 22, is known as the Philadelphia chromosome.) The combination results in the cancer gene known as BCR-ABL. This is the gene that instructs the body to make too many mature WBCs.
Although researchers know what genes are involved in the development of CML, they do not yet know why some people get it and others do not.

In CML, the body makes an uncontrolled number of abnormal blood cells. In almost all patients with CML:

- Inside a cell, pieces of two separate chromosomes break off and join together, forming an abnormal chromosome called the Philadelphia chromosome (or Ph chromosome)
- The Philadelphia chromosome then makes an abnormal protein called BCR-ABL
- The BCR-ABL protein causes the uncontrolled production of CML cells in the blood
- When one has CML, the BCR-ABL protein causes the bone marrow to produce more white blood cells, even when they are not needed. These are mostly damaged or immature. Over time, these extra, unhealthy white blood cells overcrowd healthy white blood cells, red blood cells, and platelets. The immature white blood cells are called blast cells, or blasts.

White blood cells help to fight infection. There are two different types of white blood cell lymphoid cells (lymphocytes) and myeloid cells. CML affects the myeloid cells.

Normally the white blood cells, which are produced in the bone marrow, repair and reproduce themselves in an orderly and controlled way. In leukaemia, however, the process gets out of control and the cells continue to divide but do not mature.

These immature dividing cells – known as blast cells - fill up the bone marrow and stop it making healthy blood cells. As the blast cells are immature, they cannot work properly. This puts the child at increased risk of infection. The overproduction of white blood cells also interferes with the production of healthy red blood cells and platelets, leading to symptoms such as anaemia and bruising. In contrast to the acute leukaemias, this happens very slowly in CML.

There are three different stages in the development of CML:

- Chronic phase. There may be no symptoms of leukaemia, but blast cells are present in the blood and bone marrow. This phase can last several years before undergoing transformation to the second, accelerated phase.
- Accelerated phase. An increased number of blast cells are found in the blood and marrow and there is evidence that the number of normal cells is decreasing. This phase lasts three to nine months.
• Blast phase. Also called a ‘blast crisis’. During the third and final phase, the disease resembles acute leukaemia. More than 30 per cent of bone marrow and blood cells are blast cells. Without effective treatment (see below) the disease is usually fatal within three to six months of entering the blast phase.

Millot, F., Dupraz, C., Guilhot, J., Suttrop, M., Brizard, F., Leblanc, T., Güneş, A.M., Sedlacek, P., De Bont, E., Li, C.K., Kalwak, K., Lausen, B., Culic, S., Dworzak, M., Kaiserova, E., De Moerloose, B., Roula, F., Biondi, A., Baruchel, A. & Guilhot, F. 2017. BACKGROUND: In the adult population with newly diagnosed chronic myeloid leukemia (CML), variant translocations are usually not considered to be impairing the prognosis, whereas some additional cytogenetic abnormalities (ACAs) are associated with a negative impact on survival. Because of the rarity of CML in the pediatric population, such abnormalities have not been investigated in a large group of children with CML.

METHODS: The prognostic relevance of variant t(9;22) and ACAs at diagnosis was assessed in 301 children with CML in the chronic phase who were enrolled in the International Registry for Chronic Myeloid Leukemia in Children and Adolescents.

RESULTS: Overall, 19 children (6.3%) presented with additional cytogenetic findings at diagnosis: 5 children (1.7%) had a variant t(9;22) translocation, 13 children (4.3%) had ACAs, and 1 had both. At 3 years, for children with a classic translocation, children with ACAs, and children with a variant t(9;22) translocation who were treated with imatinib as frontline therapy, the probability of progression-free survival (PFS) was 95% (95% confidence interval [CI], 91%–97%), 100%, and 75% (95% CI, 13%–96%), respectively, and the probability of overall survival (OS) was 98% (95% CI, 95%–100%), 100% (95% CI, 43%–98%), and 75% (95% CI, 13%–96%), respectively. No statistical difference was observed between the patients with classic cytogenetic findings and those with additional chromosomal abnormalities in terms of PFS and OS.

CONCLUSIONS: In contrast to adults with CML, additional chromosomal abnormalities observed at diagnosis do not seem to have a significant prognostic impact. Cancer 2017; 123:3609-16. © 2017 American Cancer Society.

Little, M.P., Wakeford, R., Borrego, D., French, B., Zablotska, L.B., Adams, M.J., Allodji, R., de Vathaire, F., Lee, C., Brenner, A.V., Miller, J.S., Campbell, D., Pearce, M.S., Doody, M.M., Holmberg, E., Lundell, M., Sadetzki, S., Linet, M.S. & Berrington de González, A. 2018. BACKGROUND: Substantial evidence links exposure to moderate or high doses of ionising radiation, particularly in childhood, with increased risk of leukaemia. The association of leukaemia with exposure to low-dose (<100 mSv) radiation is less certain, although this is the dose range most relevant to the general population. We aimed to estimate the risk of leukaemia associated with low-dose radiation exposure in childhood (age <21 years).

METHODS: In this analysis of historical cohort studies, we pooled eligible cohorts reported up to June 30, 2014. We evaluated leukaemia and myeloid malignancy outcomes in these cohorts with the relevant International Classification of Diseases and International Classification of Diseases for Oncology definitions. The cohorts included had not been treated for malignant disease, had reported at least five cases of the relevant haematopoietic neoplasms, and estimated individual active bone marrow (ABM) doses. We restricted analysis to individuals who were younger than 21 years at first irradiation who had mean cumulative ABM doses of less than 100 mSv. Dose-response models were fitted by use of Poisson regression. The data were received in fully anonymised form by the statistical analyst.

FINDINGS: We identified nine eligible cohorts from Canada, France, Japan, Sweden, the UK, and the USA, including 262 573 people who had been exposed to less than 100 mSv enrolled between June 4,
1915, and Dec 31, 2004. Mean follow-up was 19·63 years (SD 17·75) and mean cumulative ABM dose was 19·6 mSv (SD 22·7). 154 myeloid malignancies were identified (which included 79 acute myeloidleukaemias, eight myelodysplastic syndromes, and 36 chronic myeloid leukaemias, in addition to other unspecified myeloid malignancies) and 40 acute lymphoblastic leukaemias, with 221 leukaemias (including otherwise unclassified leukaemias but excluding chronic lymphocytic leukaemia) identified overall. The fitted relative risks at 100 mSv were 3·09 (95% CI 1·41-5·92; \( p_{\text{trend}}=0·008 \)) for acute myeloid leukaemia and myelodysplastic syndromes combined, 2·56 (1·09-5·06; \( p_{\text{trend}}=0·033 \)) for acute myeloid leukaemia, and 5·66 (1·35-19·71; \( p_{\text{trend}}=0·023 \)) for acute lymphoblastic leukaemia. There was no clear dose-response for chronic myeloid leukaemia, which had a relative risk at 100 mSv of 0·36 (0·00-2·36; \( p_{\text{trend}}=0·394 \)). There were few indications of between-cohort heterogeneity or departure from linearity. For acute myeloidleukaemia and myelodysplastic syndromes combined and for acute lymphoblastic leukaemia, the dose-responses remained significant for doses of less than 50 mSv. Excess absolute risks at 100 mSv were in the range of 0·1-0·4 cases or deaths per 10 000 person-years.

**INTERPRETATION:** The risks of acute myeloid leukaemia and acute lymphoblastic leukaemia were significantly increased after cumulative doses of ionising radiation of less than 100 mSv in childhood or adolescence, with an excess risk also apparent for cumulative radiation doses of less than 50 mSv for some endpoints. These findings support an increased risk of leukaemia associated with low-dose exposure to radiation and imply that the current system of radiological protection is prudent and not overly protective.

**FUNDING:** National Cancer Institute Intramural Research Program, National Cancer Institute, and US National Institutes for Health.

### Incidence of Childhood Chronic Myeloid Leukaemia

In providing the incidence figures of leukaemia in South Africa, The National Cancer Registry 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:

<table>
<thead>
<tr>
<th>Group – Boys</th>
<th>Actual No of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 19 Years</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td></td>
</tr>
<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>

<table>
<thead>
<tr>
<th>Group – Girls</th>
<th>Actual No of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 19 Years</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td></td>
</tr>
<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>Group</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>Group</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.

**Signs and Symptoms of Childhood Chronic Myeloid Leukaemia (CML)**

Possible signs of Chronic Myeloid Leukaemia (CML) include tiredness, night sweats, and fever.

These and other symptoms may be caused by CML. Other conditions may cause the same symptoms. Check with your doctor if you have any of the following problems:

- Feeling very tired
- Weight loss for no known reason
- Night sweats
- Fever
- Pain or a feeling of fullness below the ribs on the left side

Sometimes CML does not cause any symptoms at all.

Most people with CML have a gene mutation (change) called the Philadelphia chromosome.

Every cell in the body contains DNA (genetic material) that determines how the cell looks and acts. DNA is contained inside chromosomes. In CML, part of the DNA from one chromosome moves to another chromosome. This change is called the "Philadelphia chromosome." It results in the bone marrow making an enzyme, called tyrosine kinase, that causes too many stem cells to become white blood cells (granulocytes or blasts). The Philadelphia chromosome is not passed from parent to child.
Diagnosis of Childhood Chronic Myeloid Leukaemia (CML)

With CML, there are usually no symptoms in the early stages. Often it may be discovered when the child is having a routine blood test for other reasons.

When symptoms do occur, they are quite general, including:

- frequent, persistent infections
- unusual bleeding and bruising
- tiredness
- paleness and
- breathlessness

There may also be bone/joint pain, abdominal pain and/or swollen lymph nodes. Children may have some or all of these symptoms.

Treatment of Childhood Chronic Myeloid Leukaemia (CML)

This leukaemia is rare in children, but it does occur. Treatment in children is similar to what is used for adults.


BACKGROUND: Chronic myeloid leukaemia (CML) is very rare in children. The aim of the study is to report the experience within the I-CML-Ped study in children and adolescents presenting at diagnosis with advanced phase disease and to describe their characteristics and outcomes.

METHODS: Of 479 children and adolescents enrolled in the international registry for childhood chronic myeloid leukaemia (I-CML-Ped Study; www.clinicaltrials.gov NCT01281735), 36 children (7.5%) presented at initial diagnosis with CML in advanced phase according to the European LeukemiaNet criteria.

RESULTS: Nineteen (4%) patients were diagnosed in accelerated phase (CML-AP), and among the 17 patients (3.5%) diagnosed in blastic phase (CML-BP), 70% presented with lymphoid immunophenotype. Initial treatment of CML-AP/CML-BP consisted of tyrosine kinase inhibitors (TKIs) with or without chemotherapy, leading to complete haematologic response in 33 of 36 (92%) patients. Seventeen patients proceeded to haematopoietic stem cell transplantation. At the last follow-up, 18 of 19 patients with de novo CML-AP are alive in at least major molecular response (MMR) (n = 16), in progression (n = 1) or in molecular relapse (n = 1) and 13 of 17 patients with de novo CML-BP are alive in at least MMR. Five-year overall survival rates are 94% (95% confidence interval [CI]: 66%-99%) and 74% (95% CI: 44%-89%) for patients diagnosed in CML-AP and CML-BP, respectively.

CONCLUSION: Children with advanced phase at diagnosis of CML seem to have a better survival rate than that reported for advanced phases evolving under TKI treatment.


BACKGROUND: To date, no data on the adherence to specific guidelines for children with chronic myeloid leukemia (CML) in chronic phase (CP) have been reported.

METHODS: Since 2001, guidelines for treatment with imatinib mesylate (IM) and monitoring in patients younger than 18 years with CP-CML have been shared with 9 pediatric referral centers (P
centers) and 4 reference centers for adults and children/adolescents (AP centers) in Italy. In this study, the adherence to these guidelines was analyzed.

**RESULTS:** Thirty-four patients with a median age of 11.4 years and 23 patients with a median age of 11.0 years were managed at 9 P and at 4 AP centers, respectively. Evaluations of bone marrow (BM) and/or peripheral blood (PB) were available for more than 90% of evaluable patients. Cytogenetics and molecular monitoring of PB were more consistently performed in AP centers, whereas molecular analysis of BM was carried out more frequently in P centers. Before 2009, some patients who responded to IM underwent a transplantation, contrary to the guidelines' recommendations.

**CONCLUSIONS:** Our experience shows that having specific guidelines is an important tool for an optimal management of childhood CP-CML, together with exchange of knowledge and proactive discussions within the network.

Targeted therapy, such as imatinib (Gleevec) and dasatinib (Sprycel), attack cells with the Philadelphia chromosome, which is the key gene abnormality in CML. These drugs are usually very effective at controlling CML, often for long periods of time and with less severe side effects than chemotherapy drugs. However, these drugs do not seem to cure CML when used alone, and they must be taken every day.

Imatinib is usually the drug tried first. If it does not work or if it becomes less effective over time, another drug may be tried. If targeted drugs are no longer helpful, high-dose chemotherapy with a stem cell transplantation offers the best chance for a cure. Doctors are now studying whether adding targeted drugs to stem cell transplant regimens can help increase cure rates.

Imatinib mesylate has shown a high level of activity in children with CML that is comparable to that observed in adults, with approximately 75% achieving a complete cytogenetic response and with approximately 20% showing an unsatisfactory response to imatinib. The pharmacokinetics of imatinib mesylate in children appears consistent with prior results in adults. Doses of imatinib mesylate used in phase II trials for children with CML have been 260 mg/m$^2$ to 340 mg/m$^2$, which provide comparable drug exposures as the adult flat doses of 400 mg to 600 mg. Because there are no paediatric-specific data regarding optimal timing of monitoring for BCR-ABL transcript levels and for the presence of BCR-ABL kinase domain mutations, the monitoring guidelines described above for adults with CML are reasonable to utilise.

Imatinib mesylate is generally well tolerated in children, with adverse effects usually being mild to moderate and quickly reversible with treatment discontinuation or dose reduction. Growth retardation occurs in some children receiving imatinib mesylate. The growth inhibitory effects of imatinib mesylate appear to be most pronounced in prepubertal children, compared with pubertal children; children receiving imatinib mesylate and experiencing growth impairment may show a return to normal growth rates when they reach puberty.

In children who develop a hematologic or cytogenetic relapse on imatinib mesylate or who have an inadequate initial response to imatinib mesylate, determination of BCR-ABL kinase domain mutation status should be considered to help guide subsequent therapy. Depending upon the patient’s...
mutation status, alternative kinase inhibitors such as dasatinib or nilotinib can be considered based on adult experience with these agents.

An important question is the impact of imatinib mesylate treatment on outcome for patients who subsequently proceed to allogeneic HSCT. A retrospective study that compared 145 patients who received imatinib mesylate before transplant with a historical cohort of 231 patients who did not showed no difference in early hepatic toxic effects or engraftment delay. In addition, OS, disease-free survival, relapse, and nonrelapse mortality were similar between the two cohorts. The only factor associated with poor outcome in the cohort that received imatinib mesylate was a poor initial response to imatinib mesylate.

Further evidence for a lack of effect of pretransplant imatinib mesylate on posttransplant outcomes was supplied by a report from the Center for International Blood and Marrow Transplant Research comparing outcomes for 181 pediatric and adult subjects with CML in first chronic phase treated with imatinib mesylate before HSCT with that for 657 subjects who did not receive the agent before HSCT.

Among the patients in first chronic phase, imatinib mesylate therapy before HSCT was associated with better OS. A third report of imatinib followed by allogeneic HSCT supports the efficacy of this transplantation strategy in patients with imatinib mesylate failure in first chronic phase; the 3-year OS rate was 94% for this group (n = 37), with approximately 90% achieving a complete molecular remission after HSCT. The available data suggest that imatinib mesylate before transplant does not have a deleterious effect on outcome.


“A total of 156 patients (age range 1.3-18.0 years, median 13.2 years; 91 (58.3%) male) with newly diagnosed CML (N = 146 chronic phase (CML-CP), N = 3 accelerated phase (CML-AP), N = 7 blastic phase (CML-BP)) received imatinib up-front (300, 400, 500 mg/m², respectively) within a prospective phase III trial. Therapy response, progression-free survival, causes of treatment failure, and side effects were analyzed in 148 children and adolescents with complete data. Event-free survival rate by 18 months for patients in CML-CP (median follow-up time 25 months, range: 1-120) was 97% (95% CI, 94.2-99.9%). According to the 2006 ELN-criteria complete hematologic response by month 3, complete cytogenetic response (CCyR) by month 12, and major molecular response (MMR) by month 18 were achieved in 98, 63, and 59% of the patients, respectively. By month 36, 86% of the patients achieved CCyR and 74% achieved MMR. Thirty-eight patients (27%) experienced imatinib failure because of unsatisfactory response or intolerance (N = 9). In all, 28/148 patients (19%) underwent stem cell transplantation (SCT). In the SCT sub-cohort 2/23 patients diagnosed in CML-CP, 0/1 in CML-AP, and 2/4 in CML-BP, respectively, died of relapse (N = 3) or SCT-related complications (N = 2). This large pediatric trial extends and confirms data from smaller series that first-line imatinib in children is highly effective.”

Dasatinib
During November 2017 the Food and Drug Administration granted regular approval to dasatinib (SPRYCEL, Bristol-Myers Squibb Co.) for the treatment of paediatric patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukaemia (CML) in the chronic phase.
Approval was based on data from 97 paediatric patients with chronic phase CML evaluated in two trials—a phase 1, open-label, non-randomized, dose-ranging trial and a phase 2, open-label, non-randomized trial. Fifty-one patients exclusively from the phase 2 trial were newly diagnosed with chronic phase CML and 46 patients (17 from the phase 1 trial and 29 from the phase 2 trial) were resistant or intolerant to previous treatment with imatinib. The majority of patients were treated with dasatinib tablets 60 mg/m² once daily. Patients were treated until disease progression or unacceptable toxicity.

After 24 months of treatment, 96.1% of newly diagnosed patients (95% CI: 86.5, 99.5) and 82.6% of patients resistant or intolerant to imatinib (95% CI: 68.6, 92.2) had complete cytogenic response (CCyR). With a median follow-up of 4.5 years in newly diagnosed patients and 5.2 years in imatinib-resistant or -intolerant patients, the median durations of CCyR, major cytogenic response (MCyR), and major molecular response (MMR) could not be estimated as more than half of the responding patients had not progressed at the time of data cut-off.

Adverse reactions reported in ≥10% of dasatinib-treated paediatric patients (n=97) were headache, nausea, diarrhoea, skin rash, vomiting, pain in extremity, abdominal pain, fatigue, and arthralgia.

The recommended dose of dasatinib in paediatric patients is based on body weight.

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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Sources and References Consulted or Utilised

**American Cancer Society**

**Children with Cancer UK**
http://www.childrenwithcancer.org.uk/chronic-myeloid-leukaemia

**Chronic Myeloid Leukaemia**


**Childhood Leukaemia**

[Consulted or Utilised]

**Children with Cancer UK**
http://www.childrenwithcancer.org.uk/chronic-myeloid-leukaemia

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