Cancer Association of South Africa (CANSA)

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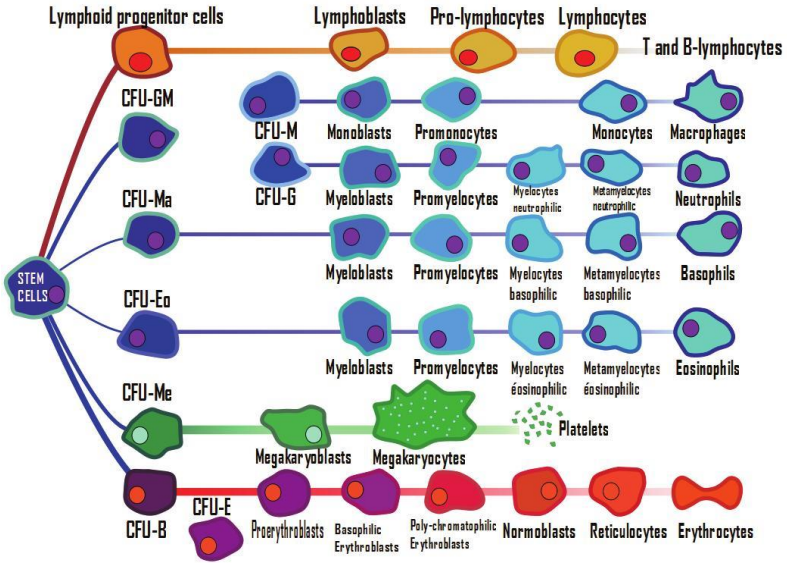
Fact Sheet
on
Juvenile Myelomonocytic Leukaemia (JMML)

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.

Lasho, T. & Patnaik, M.M. 2020.

"Juvenile myelomonocytic leukemia (JMML) is a pediatric myelodysplastic/myeloproliferative neoplasm overlap syndrome with sustained peripheral blood monocytosis, aggressive features, and poor outcomes. In >90% of cases JMML is driven by germline or somatic mutations involving the canonical RAS pathway (PTPN11, NRAS, CBL, KRAS and NF1), with somatic mutations/alterations in RAS pathway genes (second hit), SETBP1, ASXL1 and JAK3 resulting in disease progression. While spontaneous regression has been seen in germline PTPN11 and CBL mutant JMML, in most patients, allogeneic stem cell transplant is the only curative modality. JMML shares several phenotypic features with its adult counterpart proliferative, chronic myelomonocytic leukemia (pCMML). pCMML largely occurs due to RAS pathway mutations that occur in the context of age related clonal

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hematopoiesis (TET2, SRSF2, ASXL1), while JMML is a bona fide RASopathy, with additional somatic mutations, including in epigenetic regulators genes resulting in disease progression."

Synonyms of Juvenile Myelomonocytic Leukaemia

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 (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 (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	4	1	2
White boys	3	1	2	3

Group - Girls 2017	0 – 4 Years	5 – 9 Years	10 – 14 Years	15 – 19 Years
All girls	11	17	5	7
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.

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

Yoshida, N., Sakaguchi, H., Yabe, M., Hasegawa, D., Hama, A., Hasegawa, D., Kato, M., Noguchi, M., Terui, K., Takahashi, Y., Cho, Y., Sato, M., Koh, K., Kakuda, H., Shimada, H., Hashii, Y., Sato, A., Kato, K., Atsuta, Y., Watanabe, K. & Pediatric Myelodysplastic Syndrome Working Group of the Japan Society for Hematopoietic Cell Transplantation. 2020.

"Hematopoietic stem cell transplantation (HSCT) is the only curative treatment for juvenile myelomonocytic leukemia (JMML), but few large studies of HSCT for JMML exist. Using data from the Japan Society for Hematopoietic Cell Transplantation registry, we analyzed the outcomes of 129

children with JMML who underwent HSCT between 2000 and 2011. The 5-year overall survival (OS) rate and cumulative incidence of relapse were 64% and 34%, respectively. A regimen of busulfan/fludarabine/melphalan was the most commonly used (59 patients) and provided the best outcomes; the 5-year OS rate reached 73%, and the cumulative incidences of relapse and transplantation-related mortality were 26% and 9%, respectively. In contrast, the use of the irradiation-based myeloablative regimen was the most significant risk factor for OS (hazard ratio [HR], 2.92; P = .004) in the multivariate model. In addition, chronic graft-versus-host disease (GVHD) was strongly associated with lower relapse (HR, 0.37; P = .029) and favorable survival (HR, 0.22; P = .006). The current study has shown that a significant proportion of children with JMML can be cured with HSCT, especially those receiving the busulfan/fludarabine/melphalan regimen. Based on the lower relapse and better survival observed in patients with chronic GVHD, additional treatment strategies that focus on enhancing graft-versus-leukemia effects may further improve survival."

Marcu, A., Colita, A., Radu, L.E., Jercan, C.G., Bica, A.M., Asan, M., Coriu, D., Tanase, A.D., Diaconu, C.C., Mambet, C., Botezatu, A., Pasca, S., Teodorescu, P., Anton, G., Gurban, P. & Colita, A. 2020.
Background: Juvenile myelomonocytic leukemia (JMML) is a rare myelodysplastic/myeloproliferative neoplasm diagnosed in young children, characterized by somatic or germline mutations that lead to hyperactive RAS signaling. The only curative option is hematopoietic stem cell transplantation (HSCT). Recent data showing that aberrant DNA methylation plays a significant role in pathogenesis and correlates with clinical risk suggest a possible benefit of hypomethylating agents (HMA) in JMML treatment. **Aim:** The aim is to report the results of HMA-based therapy with 5-azacytidine (AZA) in three JMML patients treated in a single center, non-participating in EWOG-MDS study. **Methods:** The diagnosis and treatment response were evaluated according to international consensus criteria. AZA 75 mg/m^2 intravenous (i.v.) was administered once daily on days 1-7 of each 28-day cycle. All patients were monitored for hematologic response, spleen size, and evolution of extramedullary disease. Targeted next generation sequencing (NGS) were performed after the 3rd AZA cycle and before SCT to evaluate the molecular alterations and genetic response. **Results:** Three patients diagnosed with JMML were treated with AZA (off-label indication) in Pediatric Department of Fundeni Clinical Institute, Bucharest, Romania between 2017 and 2019. There were two females and one male with median age 11 months, range 2-16 months. The cytogenetic analysis showed normal karyotype in all patients. Molecular analysis confirmed KRAS G13D mutation in two patients and NRAS G12D mutation in one patient. The clinical evaluation showed important splenomegaly and hepatomegaly in all 3 pts. One patient received AZA for early relapse after haploidentical HSCT and the other two patients received upfront AZA, as bridging therapy before HSCT. After HMA therapy, 2/3 patients achieved clinical partial response (cPR), 1/3 had clinical stable disease (cSD) and all had genetic stable disease (gSD) after 3 cycles and were able to receive the planned HSTC. One patient achieved clinical and genetic complete response before HSCT. During 22 cycles of AZA there were only four adverse events but only one determined dose reduction and treatment delay. **Conclusion:** Our data show that AZA monotherapy is safe and effective in controlling disease both in upfront and relapsed patients in order to proceed to HSCT.

Cheng, S.Q., Zhu, X.Y., Tang, B.L., Liu, H.L., Yao, W., Sun, G.Y. & Sun, Z.M. 2020.
Objective: To explore the clinical efficacy and safety of unrelated umbilical cord blood transplantation (UCBT) in the treatment of Juvenile myelomonocytic leukemia (JMML).
Methods: The clinical data of 5 children with JMML who were treated with unrelated UCBT from October 2011 to July 2019 were retrospectively analyzed. The age of onset for the five children (male) ranged from 0.4 to 5.0 years old, with a median age of 1.5 years old. All the patients received myeloablative conditioning regimen without ATG to whom cyclosporine A (CsA) with short-term mycophenolate mofetil (MMF) was given for GVHD prophylaxis.

Results: Four children acquired engraftment. One patient received secondary haploidentical hematopoietic stem cell transplantation because of the failure in the first unrelated UCBT. Grade Ⅲ to Ⅳ aGVHD occurred in 2 cases and was controlled, and none of the patients developed cGVHD. Three cases achieved long-time disease free survival, and no patient relapsed.
Conclusion: UCBT is an effective treatment for children with JMML.

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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