

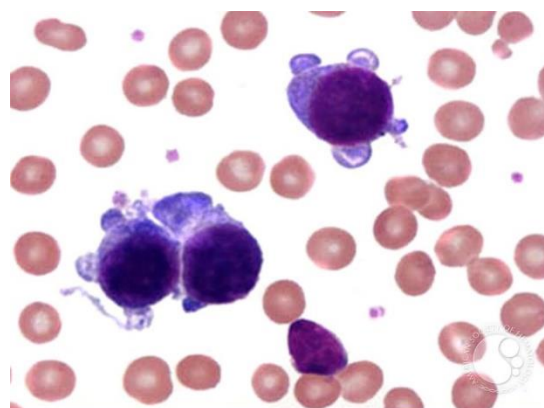
Cancer Association of South Africa (CANSA)



Fact Sheet on Acute Megakaryoblastic Leukaemia

Introduction

Acute megakaryoblastic leukemia (AMKL) is life-threatening leukaemia in which malignant megakaryoblasts proliferate abnormally and injure various tissues. Megakaryoblasts are the most immature precursor cells in a platelet-forming lineage; they mature to promegakaryocytes and, ultimately, megakaryocytes which cells shed membrane-enclosed particles, i.e. platelets, into the circulation. Platelets are critical for the normal clotting of blood.



[Picture Credit: Acute Megakaryoblastic Leukaemia]

While malignant megakaryoblasts usually are the predominant proliferating and tissue-damaging cells, their similarly malignant descendants, promegakaryocytes and megakaryocytes, are variable contributors to the malignancy.

Megakaryoblastic Leukaemia

Acute Megakaryoblastic Leukemia (AMKL) is a rare subtype of Acute Myeloid Leukaemia (AML) characterised by abnormal megakaryoblasts that express platelet-specific surface glycoprotein. Bone marrow biopsy frequently demonstrates extensive myelofibrosis, often making aspiration in these patients difficult.

AMKL is extremely rare in adults, occurring in only 1% of AML patients. This is in contrast to children, where it comprises between 4% and 15% of AML patients. It occurs more frequently among females.

In paediatrics, the disease is divided into 2 major subgroups: AMKL in patients with Down syndrome (DS-AMKL) and AMKL in patients without DS (non-DS-AMKL). AMKL is the most frequent type of AML

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in children with DS, and the incidence in these patients is 500-fold higher than in the general population.

In contrast to non-DS-AMKL, leukaemic cells carry not only megakaryocytic cell-surface markers but also erythroid markers, resulting in the distinct World Health Organization classification “myeloid leukaemia in Down syndrome”. Somatic mutations in *GATA1* are found in almost all cases of DS-AMKL and precede the development of leukaemia, as indicated by their presence in patients with transient myeloproliferative disease (TMD) in the neonatal period. DS-AMKL is both biologically and clinically distinct, with superior outcomes compared with non-DS-AMKL. Paediatric non-DS-AMKL is a heterogeneous group of patients, a significant proportion of whom carry chimeric oncogenes including *RBM15-MKL1*, *CBFA2T3-GLIS2*, *NUP98-KDM5A*, and *MLL* gene rearrangements.

It is also known as:

- Acute myeloblastic leukaemia type 7
- Acute megakaryocytic leukaemia
- Acute myeloid leukaemia M7
- AMKL
- AML M7

Garnett, C., Hernancez, D.C. & Vyas, P. 2020.

“Myeloid leukaemia of Down syndrome (ML-DS) is an acute megakaryoblastic/erythroid leukaemia uniquely found in children with Down syndrome (constitutive trisomy 21). It has a unique clinical course, being preceded by a pre-leukaemic condition known as transient abnormal myelopoiesis (TAM), and provides an excellent model to study multistep leukaemogenesis. Both TAM and ML-DS blasts carry acquired N-terminal truncating mutations in the erythro-megakaryocytic transcription factor *GATA1*. These result in exclusive production of a shorter isoform (*GATA1s*). The majority of TAM cases resolve spontaneously without the need for treatment; however, around 10% acquire additional cooperating mutations and transform to leukaemia, with differentiation block and clinically significant cytopenias. Transformation is driven by the acquisition of additional mutation(s), which cooperate with *GATA1s* to perturb normal haematopoiesis.”

Won, E., Gruber, T.A., Tucker, S. & Schiff, D.E. 2020.

“Pediatric acute megakaryoblastic leukemia (AMKL) is a rare subtype of acute myeloid leukemia (AML) that may be divided into two subgroups: (1) Down syndrome- (DS-) related AMKL which generally has a favorable prognosis and (2) non-DS-related AMKL which generally has a poorer outcome. We report a phenotypically normal child with AMKL with trisomy 21 (T21) and tetrasomy 21 clones. Subsequently, she was diagnosed with mosaic T21. She underwent reduced-intensity therapy with good outcome. We review the literature regarding AMKL-associated cytogenetic abnormalities and AMKL in association with DS. We suggest evaluation for mosaic T21 in phenotypically normal pediatric patients with T21-positive AML.”

Tamefusa, K., Fukutake, K., Ishida, H., Tamura, A., Endo, M., Hamamoto, K., Koga, Y., Yamada, M., Kanamitsu, K., Fujiwara, K., Washio, K. & Shimada, A. 2019.

“Acute megakaryoblastic leukemia in children without Down syndrome (non-DS AMKL) is considered to be a poor prognostic subtype in acutemyeloid leukemia. “

Masetti, R., Guidi, V., Ronchini, L., Bertuccio, N.S., Locatelli, F. & Pession, A. 2019.

“Pediatric non-Down-syndrome acute megakaryoblastic leukemia (non-DS-AMKL) is a heterogeneous subtype of leukemia that has historically been associated with poor prognosis. Until the advent of large-scale genomic sequencing, the management of patients with non-DS-AMKL was very difficult

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due to the absence of reliable biological prognostic markers. The sequencing of large cohort of pediatric non-DS-AMKL samples led to the discovery of novel genetic aberrations, including high-frequency fusions, such as CBFA2T3-GLIS2 and NUP98-KDM5 A, as well as less frequent aberrations, such as HOX rearrangements. These new insights into the genetic landscape of pediatric non-DS-AMKL has allowed refining the risk-group stratification, leading to important changes in the prognostic scenario of these patients. This review summarizes the most important molecular pathogenic mechanisms of pediatric non-DS-AMKL. A critical discussion on how novel genetic abnormalities have refined the risk profile assessment and changed the management of these patients in clinical practice is also provided.”

Myeloid leukaemia associated with Down syndrome:

- Occurs usually in the first four years of life.
- Average age of diagnosis is 1.8 years.
- White cell counts are often lower.

Incidence of Megakaryoblastic Leukaemia

In providing the incidence figures of Leukaemia in South Africa, the outdated National Cancer Registry (2016) does not make provision for the reporting of the different types of Leukaemia – it also does not differentiate between acute and chronic Leukaemia - neither does it provide for different statistics for cases of adult and childhood Leukaemia - except in the ‘Frequency of Histologically Diagnosed Cancer in South Africa’ Section of the Registry .

According to the National Cancer Registry (2016) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2016:

Group - Males 2016	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	264	1:801	0,68%
Asian males	10	1:659	1,02%
Black males	135	1:1 233	1,03%
Coloured males	17	1:1 105	0,33%
White males	102	1:354	0,48%

Group - Females 2016	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	227	1:1 107	0,54%
Asian females	9	1:798	0,72%
Black females	117	1:1 846	0,59%
Coloured females	21	1:844	0,41%
White females	80	1:465	0,49%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2016 was as follows (National Cancer Registry, 2016):

Group - Males 2016	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	156	15	28	20	46	34	53	12
Asian males	1	0	1	1	1	3	2	0
Black males	45	11	22	10	18	15	13	1
Coloured males	1	1	2	3	4	2	4	0
White males	8	3	3	6	23	14	34	11

Group - Females 2016	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	38	26	17	26	31	37	37	15
Asian females	2	0	0	1	2	3	1	0
Black females	31	22	11	12	16	13	10	2
Coloured females	1	3	1	3	2	3	8	0
White females	4	1	5	10	11	18	18	13

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 males' and 'all females', however, always reflect the correct totals.

Risk Factors for Megakaryoblastic Leukaemia

Acute Megakaryoblastic Leukaemia (AMKL) can occur for the following reasons:

- As a new disease
- Due to a 'secondary effect' of previous chemotherapy treatment
- As a progression from myeloproliferative cancer or myelodysplastic syndrome

Signs and Symptoms of Megakaryoblastic Leukaemia

Nonspecific symptoms may be irritability, weakness, and dizziness while specific symptoms include pallor, fever, mucocutaneous bleeding, hepatosplenomegaly, neurological manifestations and rarely lymphadenopathy. Acute panmyelosis with myelofibrosis may also be associated with AMKL.

Diagnosis of Megakaryoblastic Leukaemia

The diagnostic process includes:

- If the percentage of blast cells was >20% in the bone marrow of nucleated cells, and cell morphology was demonstrated to be megakaryoblasts, as demonstrated using a bone marrow smear, the diagnosis was AMKL. For this diagnosis, the results of flow cytometry or immunocytochemical staining were required to increase the accuracy of the diagnosis.
- If the bone marrow aspiration could not indicate a diagnosis of AMKL, detection methods of flow cytometry and immunocytochemical staining were vital, and the final diagnosis was frequently determined by positive platelet-specific antigens.
- iii) If the bone marrow aspiration diagnosis was not successful due to MF, a bone marrow biopsy was the primary test method, and the final diagnosis was determined by immunocytochemical staining for factor VIII, CD41, CD42 or CD61.

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Treatment of Megakaryoblastic Leukaemia

Despite recent improvements in the understanding of the causes of AMKL, the optimal treatment is still debated. Currently there is no 'targeted therapy' available for AMKL.

Some haematologists treat children with AMKL but without Down syndrome as very high-risk and recommend an allogeneic stem cell transplant as soon as complete remission has been achieved. However, others treat these children with intensive chemotherapy only, and have achieved excellent survival rates.

Nevertheless, treatment protocols nearly always include cytarabine and an anthracycline; originally produced as an antibiotic.

The prognosis for children with AMKL but not Down syndrome is controversial. Although, the prognosis tends to be worse than for other forms of AMKL.

Prognostic factors can include:

- The gene *inv(16) CBFA2T3-GLIS2* – patients with this gene are predicted a poor outcome.
- The *t(1;22)* translocation – as long as intensive chemotherapy and adequate supportive care is provided, patients could have a favourable prognosis.

Feng, J., Leung, A.W.K., Cheng, F.W.T., Lam, G.K.S., Chow, T.T.W., Ng, M.H.L., Chu, W.C.W., Chan, N.P.H. & Li, C.K. 2020.

Background: There is no established effective treatment for patients with *t(1;22)(p13;q13)* acute megakaryoblastic leukemia (AMKL) and hepatic fibrosis.

Observation: Here we report the outcomes of 2 *t(1;22)(p13;q13)* AMKL patients with hepatic fibrosis. One patient died from liver failure despite the control of leukemia. The other patient was successfully treated with reduced-intensity chemotherapy and antifibrosis therapy with tretinoin and α -tocopheryl acetate, the hepatic fibrosis resolved and leukemia was in remission for 3 years.

Conclusions: Reduced-intensity chemotherapy plus antifibrosis therapy with tretinoin and α -tocopheryl acetate could be a treatment option for these patients with *t(1;22)(p13;q13)* AMKL and hepatic fibrosis.

Wang, M., Zhang, T., Zhang, X., Jiang, Z., Peng, M. & Huang, Z. 2020.

Background: Forced polyploidization is an effective strategy for acute megakaryoblastic leukemia (AMKL) therapy and factors controlling polyploidization are potential targets for drug development. Although bone morphology protein 2-inducible kinase (BMP2K) has been implied to be a potential target for fasudil, a potent polyploidy-inducing compound, the function of BMP2K in megakaryopoiesis and AMKL remains unknown. This study aimed to investigate the role of BMP2K as a novel regulator in megakaryocyte polyploidization and differentiation and its implication in AMKL therapy.

Results: BMP2K upregulation was observed in human megakaryopoiesis and leukemia cells whereas BMP2K was downregulated in AMKL cells forced to undergo terminal differentiation. Functionally, BMP2K suppressed MLN8237-induced megakaryocytic differentiation in AMKL cells and dampened megakaryocyte differentiation in primary mouse fetal liver cells. Furthermore, BMP2K overexpression conferred resistance to multiple chemotherapy compounds in AMKL cells. Mechanistically, cyclin-dependent kinase 2 (CDK2) interacted with BMP2K and partially mediated its function. In transient MLN8237 and nocodazole challenge cell model, BMP2K reduced cell percentage of G2/M phase but

increased G1 phase, suggesting a role of BMP2K antagonizing polyploidization and promoting mitosis by regulating cell cycle in megakaryopoiesis.

Conclusions: BMP2K negatively regulates polyploidization and megakaryocyte differentiation by interacting CDK2 and promoting mitosis in megakaryopoiesis. BMP2K may serve as a potential target for improvement of AMKL therapy.

De Marchi, F., Araki, M. & Komatsu, N. 2019.

“Acute megakaryoblastic leukemia (AMeGL) is a rare hematological neoplasm most often diagnosed in children and is commonly associated with Down's syndrome (DS). Although AMeGLs are specifically characterized and typically diagnosed by megakaryoblastic expansion, recent advancements in molecular analysis have highlighted the heterogeneity of this disease, with specific cytogenetic and genetic alterations characterizing different disease subtypes. Areas covered: This review will focus on describing recurrent molecular variations in both DS and non-DS pediatric AMeGL, their role in promoting leukemogenesis, their association with different clinical aspects and prognosis, and finally, their influence on future treatment strategies with a number of specific drugs beyond conventional chemotherapy already under development. Expert opinion: Deep understanding of the genetic and molecular landscape of AMeGL will lead to better and more precise disease classification in terms of diagnosis, prognosis, and possible targeted therapies. Development of new therapeutic approaches based on these molecular characteristics will hopefully improve AMeGL patient outcomes.”

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/

Medical Disclaimer

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