Cancer Association of South Africa (CANSA)

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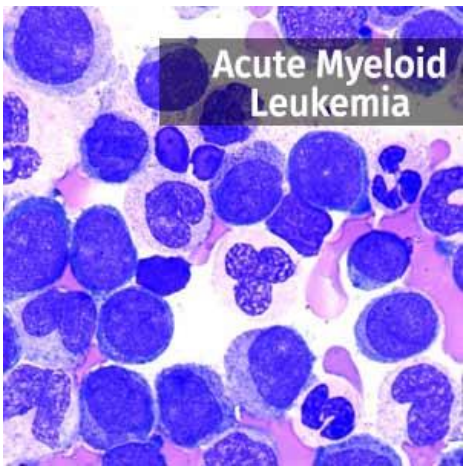
Fact Sheet on Adult Acute Myeloid Leukaemia (AML)

Introduction

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: Acute Myeloid Leukaemia Bone Marrow Aspirate]

Adult Acute Myeloid Leukaemia (AML)

It is said that adult Acute Myeloid Leukaemia (AML) is the most common type of acute leukaemia diagnosed in adults. This could, however, not be confirmed for South Africa as the National Cancer Registry does not differentiate between the different cancers – all leukaemias are listed in combined fashion.

Incidence of Adult Acute Myeloid Leukaemia (AML)

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 - 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 (2014) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2014:

Group - Males 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	366	1:598	1,99%
Asian males	8	1:1 041	0,99%
Black males	163	1:1 264	1,47%
Coloured males	54	1:313	1,29%
White males	140	1:225	0,68%

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Group - Females 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	258	1:1 069	0,68%
Asian females	12	1:1 607	1,04%
Black females	118	1:2 104	0,73%
Coloured females	36	1:684	0,88%
White females	91	1:363	0,56%

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

Group - Males 2014	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	81	28	30	46	48	74	39	17
Asian males	1	1	1	1	0	3	1	0
Black males	49	18	19	25	18	20	5	2
Coloured males	12	4	3	5	9	10	8	2
White males	12	5	6	18	18	23	30	11

Group - Females 2014	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	54	30	24	36	37	40	26	10
Asian females	2	1	0	4	0	4	0	0
Black females	28	22	14	19	16	10	4	2
Coloured females	10	2	3	2	5	8	2	3
White females	12	5	5	10	16	16	20	5

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.

Causes of Adult Acute Myeloid Leukaemia (AML)

In most cases the causes of AML remain largely unknown but it is thought to result from damage to one or more of the genes that normally control blood cell development. Research is going on all the time into finding possible causes. Certain factors have been identified that may put some people at an increased risk.

A study was conducted in the United States of America (Tsai, *et al*., 2014) into occupations and adult acute myeloid leukaemia (AML) – no corresponding research or information could be found for South Africa.

Individuals working in the following sectors had an increased risk of AML:

- Agriculture, forestry, fishing and hunting
- Non-durable goods manufacturing
- Healthcare support occupations
- Building and grounds cleaning and maintenance occupations
- Farming, fishing and forestry occupations
- Construction and extraction occupations
- Installation, maintenance and repair occupations
- Production occupations

Risk Factors for Adult Acute Myeloid Leukaemia (AML)
Anything that increases one's risk of getting a disease is called a risk factor. Having a risk factor does not mean that one will get cancer; not having risk factors does not mean that one will not get cancer.

Possible risk factors for AML include the following:

- Being male.
- Smoking, especially after age 60.
- Having had treatment with chemotherapy or radiation therapy in the past.
- Having had treatment for childhood acute lymphoblastic leukaemia (ALL) in the past.
- Being exposed to radiation from an atomic bomb or to the chemical benzene.
- Having a history of a blood disorder such as myelodysplastic syndrome.

Signs and Symptoms of Adult Acute Myeloid Leukaemia (AML)
Typically AML comes on suddenly, within days or weeks. Less often, a patient has been ill for a few months or may have a prior history of Myelodysplastic Syndrome.

AML makes people sick primarily by interfering with normal bone marrow function. The leukaemia cells replace and crowd out the normal cells of the bone marrow, thereby causing low blood cell counts. This insufficient number of red blood cells results in a condition called anaemia, which causes a person to be tired and pale. Lack of platelets can make one more susceptible to bleeding and bruising, especially in the skin, nose and gums. Lowered levels of normal white blood cells increase the risk of infection.

Although infections can be of any type, typical symptoms include:

- Fever
- Lethargy and fatigue
- Pale skin
- Easy bruising
- Swollen lymph nodes
- Swollen gums
- Unusual bleeding, such as frequent nosebleeds and bleeding from the gums
- Bone pain
- Abdominal discomfort due to swollen liver or spleen
- Infections of the bloodstream, called sepsis

Mądry, K., Lis, K., Biecek, P., Młynarczyk, M., Rytel, J., Górka, M., Kacprzyk, P., Dutka, M., Rodzaj, M., Bołkun, Ł., Krochmalczyk, D., Łątka, E., Drozd-Sokołowska, J., Waszczuk-Gajda, A., Knopińska-Posłuszny, W., Kopińska, A., Subocz, E., Masternak, A., Guzicka-Kazimierczak, R., Gil, L., Machowicz, R., Biliński, J., Giebel, S., Czerw, T. & Dwilewicz-Trojaczek, J. 2019.
BACKGROUND: Myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), and acute myeloid leukemia (AML) patients, including those treated with azacitidine, are at increased risk for serious infections. The aim of our study was to identify patients with higher infectious risk at the beginning of azacitidine treatment.

PATIENTS AND METHODS: We performed a retrospective evaluation of 298 MDS/CMML/AML patients and included in the analysis 232 patients who completed the first 3 cycles of azacitidine therapy or developed Grade III/IV infection before completing the third cycle.
RESULTS: Overall, 143 patients (62%) experienced serious infection, and in 94 patients (41%) infection occurred within the first 3 cycles. The following variables were found to have the most significant effect on the infectious risk in multivariate analysis: red blood cell transfusion dependency (odds ratio [OR], 2.38; 97.5% confidence interval [CI], 1.21-4.79), neutropenia $<0.8 \times 10^9$/L (OR, 3.03; 97.5% CI, 1.66-5.55), platelet count $<50 \times 10^9$/L (OR, 2.63; 97.5% CI, 1.42-4.76), albumin level <35 g/dL (OR, 2.04; 97.5% CI, 1.01-4.16), and Eastern Cooperative Oncology Group performance status ≥2 (OR, 2.19; 97.5% CI, 1.40-3.54). Each of these variables is assigned 1 point, and the combined score represents the proposed Azacitidine Infection Risk Model. The infection rate in the first 3 cycles of therapy in lower-risk (0-2 score) and higher-risk (3-5 score) patients was 25% and 73%, respectively. The overall survival was significantly reduced in higher-risk patients compared with the lower-risk cohort (8 vs. 29 months).
CONCLUSION: We selected a subset with high early risk for serious infection and worse clinical outcome among patients treated with azacitidine.

Diagnosis of Adult Acute Myeloid Leukaemia (AML)
Tests that examine the blood and bone marrow are usually used to detect (find) and diagnose adult AML.

The following tests and procedures may be used:

- Physical examination and history: An examination of the body to check general signs of health, including checking for signs of disease, such as lumps or anything else that seems unusual. A history of the patient's health habits and past illnesses and treatments is also usually taken

- Complete Blood Count (CBC): A procedure in which a sample of blood is drawn and checked for the following:
    - The number of red blood cells, white blood cells, and platelets
    - The amount of haemoglobin (the protein that carries oxygen) in the red blood cells
    - The portion of the sample made up of red blood cells
- Bone marrow aspiration and biopsy
- A laboratory test in which the cells in a sample of blood or bone marrow are viewed to look for certain changes in the chromosomes
- Immunophenotyping: A process used to identify cells, based on the types of antigens or markers on the surface of the cell
- Reverse transcription–polymerase chain reaction test (RT–PCR): A laboratory test in which cells in a sample of tissue are studied using chemicals to look for certain changes in the structure or function of genes

Treatment of Adult Acute Myeloid Leukaemia (AML)
The usual treatment of AML is usually divided into two phases: induction of remission and post-remission therapy.

Induction therapy - the initial phase of treatment is referred to as remission induction or 'induction' therapy. Induction therapy is given with the goal of decreasing the number of leukaemia cells to an undetectable level and restoring the production of normal blood cells.

Complete remission — the first goal of AML treatment is to achieve a complete remission. Complete remission means that there is no visible evidence of leukaemia cells in the blood or bone marrow and the bone marrow is functioning normally. A bone marrow biopsy and blood testing are done to determine when/if this occurs.

Post-remission therapy - is given with the intention of killing leukaemia cells that can remain in the bone marrow or blood, but are undetectable under the microscope.

Additional chemotherapy — chemotherapy given after remission is called remission consolidation or post-remission chemotherapy

Stem cell transplantation — stem cell transplantation, also called bone marrow transplantation or haematopoietic stem cell transplantation

Flores-Jiménez, J.A., Pimentel-Morales, M.A., González-Ramella, O., Vega-Cortés, D. & Zambrano-Velarde, M.Á. 2019. "Acute myelogenous leukemia (AML) represents ∼33% of those in adolescents and young adults. Hematopoietic cell transplantation in its various practices has been used as a treatment for acute myeloid leukemia, especially in refractory or relapsing patients. In this study, we describe two young adults with AML who were treated at our hospital. One was refractory to conventional treatment and the other case was relapsed after a first complete remission. They achieved complete remission with new combined treatment (venetoclax + cytarabine) consolidating them with hematopoietic stem cell transplantation."

Allogeneic transplantation - uses stem cells from a healthy donor, ideally a sibling with a similar genetic makeup (called an HLA-matched related donor; MRD).

Bonifazi, F., Solano, C., Wolschke, C., Sessa, M., Patriarca, F., Zallio, F., Nagler, A., Selleri, C., Risitano, A.M., Messina, G., Bethge, W., Herrera, P., Sureda, A., Carella, A.M., Cimminiello, M., Guidi, S., Finke, J., Sorasio, R., Ferra, C., Sierra, J., Russo, D., Benedetti, E,, Milone, G., Benedetti, F., Heinzelmann, M., Pastore, D., Jurado, M., Terruzzi, E., Narni, F., Völp, A., Ayuk, F., Ruutu, T. & Kröger, N. 2019.
BACKGROUND: We previously showed that human anti-T-lymphocyte globulin (ATLG) plus ciclosporin and methotrexate given to patients with acute leukaemia in remission, having allogeneic haemopoietic stem-cell transplantation with peripheral blood stem cells from an HLA-identical sibling donor after myeloablative conditioning, significantly reduced 2-year chronic graft-versus-host disease (cGVHD) incidence and severity, without increasing disease relapse and infections, and improves cGVHD-free and relapse-free survival (cGRFS). The aim of an extended follow-up study was the assessment of long-term outcomes, which are, in this context, scarcely reported in the

literature. We report unpublished data on quality of life (QoL) from the original study and the results of a follow-up extension.

METHODS: In the original open-label study, patients with acute myeloid and lymphoblastic leukaemia in first or subsequent remission, having sibling HLA-identical allogeneic peripheral blood stem-cell transplantation, were randomly assigned (1:1) to receive ATLG plus standard GVHD prophylaxis with ciclosporin and short-term methotrexate (ATLG group) or standard GVHD prophylaxis without ATLG (non-ATLG group). Conditioning regimens were cyclophosphamide 120 mg/kg with either total body irradiation (12 Gy) or busulfan (12·8 mg/kg intravenously or 16 mg/kg orally), with or without etoposide (30-60 mg/kg). Randomisation was stratified according to centre and disease risk. The primary endpoint was cumulative incidence of cGVHD at 2 years. The primary and secondary endpoints, excluding QoL, have been published. QoL, assessed using European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-HDC29 questionnaires, was an unpublished secondary endpoint, which we now report here. A follow-up extension was then done, with the primary endpoint cumulative incidence of cGVHD. Enrolment has been completed for both studies. The original trial (number, NCT00678275) and follow-up extension (number, NCT03042676) are registered at ClinicalTrials.gov.

FINDINGS: In the original study, from Dec 14, 2006, to Feb 2, 2012, 161 patients were enrolled and 155 were randomly assigned to either the ATLG group (n=83) or to the non-ATLG group (n=72). In the follow-up study, which started on Feb 7, 2017, and was completed on June 30, 2017, 61 patients were included in the ATLG group and 53 were included in the non-ATLG group. Global health status showed a more favourable time course in the ATLG group compared with the non-ATLG group (p=0·02; treatment by visit interaction). ATLG was descriptively superior to non-ATLG at 24 months for physical function (points estimate -14·8 [95% CI -26·4 to -3·1]; p=0·014) and social function (-19·1 [-38·0 to -0·2]; p=0·047), gastrointestinal side-effects (8·8 [2·5-15·1]; p=0·008) and effect on family (13·5 [1·2-25·8]; p=0·032). Extended follow-up (median 5·9 years [IQR 1·7-7·9]) confirmed a lower 5-year cGVHD incidence (30·0% [95% CI 21·4-41·9] vs 69·1% [59·1-80·1]; analysis for entire follow-up, p<0·001), no increase in relapses (35·4% [26·4-47·5] vs 22·5% [14·6-34·7]; p=0·09), improved cGRFS (34·3% [24·2-44·5] vs 13·9% [7·1-22·9]; p=0·005), and fewer patients still in immunosuppression (9·6% vs 28·3%; p=0·017) in the ATLG group compared with the non-ATLG group. 5-year overall survival, relapse-free survival, and non-relapse mortality did not differ significantly between groups.

INTERPRETATION: The addition of ATLG to standard GVHD prophylaxis improves the probability of surviving without disease relapse and cGVHD after myeloablative peripheral blood stem-cell transplantation from an HLA-identical sibling donor for patients with acute leukaemia in remission. Further additional benefits are better QoL and shorter immunosuppressive treatment compared with standard GVHD prophylaxis without ATLG. Therefore, in this setting, ATLG plus standard GVHD prophylaxis should be preferred over the standard GVHD prophylaxis alone.

Autologous transplant – the patient's own normal stem cells are collected while in complete remission.

Hatsumi, N., Miyawaki, S., Yamauchi, T., Takeshita, A., Komatsu, N., Usui, N., Arai, Y., Ishida, F., Morii, T., Kano, Y., Ogura, M., Machida, S., Nishii, K., Honda, S., Ohnishi, K., Naoe, T. & Japan Adult Leukemia Study Group (JALSG). 2019.

"Given the poor prognosis of patients with relapsed/refractory acute myeloid leukemia (AML), better therapy is needed. Fludarabine enhances the efficacy of Ara-C (cytarabine) by increasing intracellular Ara-C-triphosphate. The FLAG (fludarabine, high-dose Ara-C, supported with

granulocyte colony-stimulating factor) regimen has been tested for use in AML patients by other investigators. In the phase II study reported here, we evaluated the efficacy and toxicity of FLAGM therapy (FLAG with mitoxantrone), further intensified by adding mitoxantrone, based on the results of a phase I study by our group. The major endpoints were complete remission (CR) rate and early death. From June 2004 to February 2008, 41 patients (median age 52 years; range 18-64 years) were enrolled. Thirty (73% 95% CI 58-84%) patients achieved CR, which met the primary endpoint; there was a single case of early death from pneumonia. Two-year overall survival was 39.4% (95% CI 25.2-55.6%). Of those who achieved CR, 27 underwent allogeneic stem cell transplantation (SCT), and 12 SCT recipients showed long-term survival. Grade 3/4 non-hematological adverse events included infection (59%), nausea/vomiting (15%), diarrhea (7%), and elevated liver enzymes (7%). In conclusion, FLAGM is an effective and safe salvage therapy for patients with relapsed/refractory AML, and facilitated SCT for a large proportion of patients."

Kanakasetty, G.B., R, C., K. C. L., Dasappa, L., Jacob, L.A., M. C. S.B., K. N. L., Haleshappa, R.A., L. K. R., Saldanha, S.C., Deepak, K., Rajesh, P. & Asati, V. 2019.
"Elderly patients with acute myeloid leukemia have a poor prognosis. Data from developing countries is sparse in the literature. In this retrospective study, 402 patients aged ≥ 60 years, diagnosed between Jan 2013 and Dec 2017, were analyzed for treatment patterns and survival. Median age of the whole cohort was 68 years (range 61-84). A total of 213 patients (53.3%) refused care; 188 patients (46.7%) received either BSC, LDAC, or HMA. Survival (in months) was 3.9, 6.4, and 1.2 with LDAC, HMA, and BSC, respectively. One-year survival was 17.2% and 6% with HMA and LDAC, respectively (P = 0.02). Overall response rate (ORR) did not differ between HMA and LDAC group (p = 0.12). HMA cohort had higher complete responses (20.6% vs 7.4%, p = 0.02), stable disease (32.7% vs 13.5%, p = 0.02), and transfusion independence (TI) (46.5% vs 22.2%, p = 0.01). Survival did not differ between the groups if the patients achieved ORR (12.3 vs 9.8 p = 0.2) or TI (11.6 vs 6.4 p = 0.2). Stable disease with HMA led to longer survival (8.1 vs 5.3 p = 0.01). HMAs were more effective than LDAC irrespective of cytogenetic risk category and blasts, of note HMAs improved survival of poor risk patients (5.6 vs 2.9 p = 0.004). HMA treatment (HR = 0.48; 95% 0.29-0.79, p = 0.004) and transfusion independence (HR = 0.2; 95% 0.1-0.3, p = 0.0001) predicted survival in multivariate analysis. Neutropenia and febrile neutropenia were frequent in HMA. Thrombocytopenia was the common adverse event with LDAC. Novel and cost-effective drugs are essential to improve the prognosis of these patients."

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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