Cancer Association of South Africa (CANSA)

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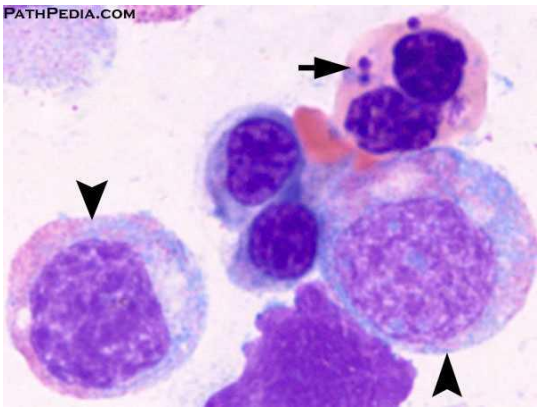
Fact Sheet
on
Acute Erythroid Leukaemia

Introduction

Erythroleukemia (or "acute Di Guglielmo syndrome") is a rare form of acute myeloid leukemia (AML) where the myeloproliferation is of erythrocyte precursors. It is defined at type "M6" under the FAB classification. M6 or erythroleukemia is rare and difficult to diagnose. More than 30-50% of the nucleated marrow cells are abnormal nucleated red blood cells.



[Picture Credit: AEL – M6]

Acute Erythroid Leukaemia

Acute erythroid leukaemia is a rare form of Acute Myeloid Laeukaemia (less than 5% of AML cases) where the myeloproliferation is of erythroblastic precursors. It is defined as type "M6" under the FAB classification.

Acute Erythroid Leukaemia is a subtype of Acute Meyeloid Leukaemia (AML) that is distinguished by erythroblastic proliferation. Patients usuallly present with nonspecific signs and symptoms from the anaemia, thrombocytopenia, and leukopenia resulting from the replacement of bone marrow by leukaemic cells.

Di Genua, C., Valletta, S., Buono, M., Stoilova, B., Sweeney, C., Rodriguez-Meira, A., Grover, A., Drissen, R., Meng, Y., Beveridge, R., Aboukhalil, Z., Karamitros, D., Belderbos, M.E., Bystrykh, L., Thongjuea, S., Vyas, P. & Nerlov, C. 2020.

"Acute erythroid leukemia (AEL) commonly involves both myeloid and erythroid lineage transformation. However, the mutations that cause AEL and the cell(s) that sustain the bilineage leukemia phenotype remain unknown. We here show that combined biallelic Cebpa and Gata2 zinc finger-1 (ZnF1) mutations cooperatively induce bilineage AEL, and that the major leukemia-initiating cell (LIC) population has a neutrophil-monocyte progenitor (NMP) phenotype. In pre-leukemic NMPs Cebpa and Gata2 mutations synergize by increasing erythroid transcription factor (TF) expression and erythroid TF chromatin access, respectively, thereby installing ectopic erythroid potential. This erythroid-permissive chromatin conformation is retained in bilineage LICs. These results demonstrate that synergistic transcriptional and epigenetic reprogramming by leukemia-initiating mutations can

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generate neomorphic pre-leukemic progenitors, defining the lineage identity of the resulting leukemia."

Santos, F.P., Faderl, S., Garcia-Manero, G., Koller, C., Beran, M., O'Brien, S., Pierce, S., Freireich, E.J., Huang, X., Borthakur, G., Bueso-Ramos, C., de Lima, M., Keating, M., Cortes, J., Kantarjian, H. & Ravandi, F. 2009.
"Acute erythroleukemia (AML-M6) is an uncommon subtype of acute myeloid leukemia (AML); it is considered to have a poor prognosis. From 1 January 1980 to 21 May 2008, 91 patients with newly diagnosed AML-M6 were seen at the University of Texas-M.D. Anderson Cancer Center (UT-MDACC). Forty-five patients (50%) had a history of myelodysplatic syndrome (MDS), compared with 41% in our control group (patients with other AML subtypes) (P=0.08). Poor-risk cytogenetics were more common in patients with AML-M6 (61% versus 38%, P=0.001). Complete remission rates were 62% for patients with AML-M6, comparing with 58% for the control group (P=0.35). Median disease free survival (DFS) for patients with AML-M6 was 32 weeks, versus 49 weeks for the control group (P=0.05). Median overall survival (OS) of patients with AML-M6 was 36 weeks, compared with 43 weeks for the control group (P=0.60). On multivariate analysis for DFS and OS, AML-M6 was not an independent risk factor. AML-M6 is commonly associated with a previous diagnosis of MDS and poor-risk karyotype. The diagnosis of AML-M6 does not impart by itself a worse prognosis, and treatment decisions on this disease should be guided by well known AML prognostic factors."

Incidence of Acute Erythroid Leukaemia
In providing the incidence figures of Leukaemia in South Africa, the outdated 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 - 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 (2017) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2017:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	338	1:634	0,85%
Asian males	7	1:1 000	0,72%
Black males	151	1:1 357	1,12%
Coloured males	29	1:862	0,58%
White males	151	1:209	0,72%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	230	1:1 289	0,55%
Asian females	8	1:1 010	0,62%
Black females	106	1:2 410	0,56%
Coloured females	25	1:1 074	0,53%
White females	91	1:455	0,52%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Males 2017	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	82	21	29	33	54	61	42	16
Asian males	0	0	3	1	1	1	1	0
Black males	66	10	19	16	16	19	4	1
Coloured males	7	2	1	4	6	3	5	1
White males	9	9	6	12	31	38	3	14

Group - Females 2017	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	40	17	20	28	31	39	37	18
Asian females	1	1	0	0	2	3	1	0
Black females	32	10	17	12	15	14	2	4
Coloured females	1	3	0	5	4	6	5	1
White females	6	3	3	11	10	16	29	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 Acute Erythroid Leukaemia

Risk factors for Acute Erythroid Leukaemia may include:

Radiation exposure - Being exposed to high levels of radiation is a risk factor for Acute Myeloid Leukaemia (AML). For example, Japanese atomic bomb survivors had a greatly increased risk of developing acute leukaemia.

Treating cancer with radiation therapy also increases the risk of leukaemia, although more for AML. The risk seems to be higher if chemotherapy and radiation are both used in treatment.

The possible risks of leukaemia from being exposed to lower levels of radiation, such as from medical imaging tests like X-rays or CT scans, are not well understood. Exposure to such radiation, especially very early in life, may carry an increased risk of leukaemia, but this is not clear. If there is an increased risk it is likely to be small, but to be safe, most doctors try to limit radiation exposure from these tests as much as possible, especially in children and pregnant women.

Certain chemical exposures - the risk of ALL may be increased by exposure to certain chemotherapy drugs and certain other chemicals, including benzene. Benzene is used in many industries to make other products, and is also in cigarette smoke, as well as some glues, cleaning products, detergents, art supplies, and paint strippers. Chemical exposure is more strongly linked to an increased risk of AML than to ALL.

Certain viral infections - infection with the human T-cell lymphoma/leukemia virus-1 (HTLV-1) can cause a rare type of T-cell ALL. Most cases occur in Japan and the Caribbean area. This disease is not common in the United States.

In Africa, the Epstein-Barr virus (EBV) has been linked to Burkitt lymphoma, as well as to a form of ALL. In the United States, EBV most often causes infectious mononucleosis ("mono").It has also been linked with a type of lymphoma that can occur after a stem cell transplant (known as post-transplant lymphoproliferative disorder, or PTLD).

Certain genetic syndromes - ALL itself doesn't appear to have a strong inherited component. That is, it doesn't seem to run in families, so a person's risk is not increased if a family member (other than an identical twin - see below) has the disease.

But there are some genetic syndromes (some of which can be inherited from a parent) that seem to raise the risk of ALL. These include:

- Down syndrome
- Klinefelter syndrome
- Fanconi anaemia
- Bloom syndrome
- Ataxia-telangiectasia
- Neurofibromatosis
- Li-Fraumeni syndrome

Age - ALL is more likely to occur in children and in adults over the age of 50.

Race/ethnicity - ALL is more common in whites than in African Americans, but the reasons for this are not clear.

Gender - ALL is slightly more common in males than in females. The reason for this is unknown.

Having an identical twin with ALL - someone who has an identical twin who develops ALL in the first year of life has an increased risk of getting ALL.

Signs and Symptoms of Acute Erythroid Leukaemia

Patients rarely present with symptoms lasting longer than 6 months, and they are usually diagnosed within 1-3 months after the onset of symptoms. The most common presenting symptoms are as follows:

- Fatigue or malaise
- Minimal-to-modest weight loss
- Easy bruising
- Fever
- Bone or abdominal pain
- Dyspnoea
- Meningeal signs and symptoms (very rare, only if leukemic involvement of the central nervous system [CNS] is present)
- Diffuse joint pain (nonspecific in one third of patients)

Ma, Z.Q., Pan, J.H., Jing, D.X. & Xu, C.Y. 2017.

"To observe the biological characteristic and the prognoses in patients with acute erythroleukemia (AEL). The results of 167 patients with newly diagnosed AEL, from January 2004 and June 2014 in the department of Hematology, Shandong Province Chinese Medicine Hospital, were reviewed by morphology, immunology, cytogenetics, molecular biology. Flow cytometry analysis indicated that CD13 (96.1 %), CD33 (95.1 %), CD117 (87.4 %) and CD34 (79.4 %) were highly expressed in AEL. 56 of 148 (37.8 %) AEL patients had a variety of cytogenetic abnormalities, 27 of 148 (18.2 %) patients were

complex karyotype (abnormal involving 3 or more chromosomes), the abnormalities of chromosomes 3, 5, 7 and 8 were more frequently involved and the most common one was +8, accounting for 35.7 % of all abnormal karyotype, followed by 5q- (17.9 %). Mutation analysis showed CEBPA mutation ratio of AEL patients was 44.0 % (11/25), that of NPM1as 15.4 % (4/26). Initial induced remission rate of AEL was 56.6 % (30/53), compared by 33.3 % (4/12) of MDSM6. Survival analysis was shown that the overall survival in female was better than that in male (P = 0.047). The overall survival time of transplantation group was significantly longer than chemotherapy group (P = 0.000). The OS of 13-39 years old group was the best, 40-49 years old group took second place, >50 years old group appeared to be the worst. Patients with AML-M_6 had dysplasia in varying degrees in granulocyte, erythrocyte and megakaryocyte series. Periodic acid-Shiff reaction staining in polychromatic erythroblast and ortho-chromatic erythroblast had a specificity in the diagnosis of AEL. AEL had its own unique biological features, and allogeneic hematopoietic stem cell transplantation could significantly improve its poor prognosis."

Diagnosis of Acute Erythroid Leukaemia

Criteria for diagnosis of Acute Erythroid Leukaemia usually includes:

Erythroleukaemia - historically, AML with erythroid features has been designated M6 by the French-American-British (FAB) group. The FAB criteria for M6 diagnosis are: bone marrow erythroblasts equal to or greater than 50% and blasts equal to or greater than 30% of the non-erythroid cells. The World Health Organization (WHO) have recently recommended that the requisite blast percentage for a diagnosis of AML be 20% or greater, and this includes erythroid leukaemia. AML M6 would equate to the new WHO definition of erythroleukaemia (erythroid/myeloid). If there are less than 20% blasts, the diagnosis is refractory anaemia with an excess of blasts (RAEB). Trilineage dysplasia is common but is not a prerequisite for diagnosis. Erythroid dysplasia may manifest as binuclearity, nucleocytoplasmic asynchrony and vacuolation. The morphological appearance of the myeloblasts is not characteristic and they may contain Auer rods. Myeloperoxidase and Sudan black B stains may be positive in the myeloblasts. The iron stain may show ringed sideroblasts and PAS may be positive in the erythroid precursors in a block or diffuse pattern.

Pure erythroid leukaemia - in addition to the typical AML M6 (erythroleukaemia), there is a second subtype of acute erythroid leukaemia where there is a neoplastic proliferation of immature cells entirely committed to the erythroid series (>80% of marrow cells) without evidence of a myeloid component. This is termed pure erythroid leukaemia by the WHO. Morphology is characterised by medium sized erythroblasts with fine nuclear chromatin, distinct nucleoli and deeply basophilic cytoplasm that often have vacuoles. Occasionally the blasts can resemble acute lymphoblastic leukaemia, distinction can be made by immunophenotyping. The erythroid nature of the blasts can be shown by electron microscopy demonstrating free ferritin particles. The blasts are negative for Sudan black B and myeloperoxidase (MPO), but positive for PAS in a block pattern.

Yin, Y., Zhan, W.Q., Huang, H.F., Zhang, C.Q., Fu, D.H., Xu, S.J., Hu, J.D. & Chen, X.J. 2017.

OBJECTIVE:

To investigate the biological characteristics and therapeutic efficacyt of acute erythroleukemia (AEL,AML-M6).

METHODS:

Blood cell count, liver function, lactate dehydrogenase level, coagulation, morphology, immunology, cell genetics and molecular biology were retrospectively analyzed in 103 cases of acute erythroleukemia patients admitted in our department from May 2016 to June 2009. The

therapeutic efficacy was observed by means of remission rate, relapse rate, relapse-free survival and overall survival.

RESULTS:

The medians of white blood cells, granulocyte, hemoglobin and platelet were 3.04×10^9/L, 0.67×10^9/L, 66 g/L, and 45×10^9/L,respectively. Nucleated red blood cells were found in the peripheral blood smears from 71.1% of AEL patients. None of the patients showed abnormal coagulation function. Flow cytometry analysis indicated that CD13 (93.5%),CD117(89.1%), HLA-DR(87.0%), and CD34 (80.0%) were highly expressed in AEL, and lymphoid antigens of CD4 (42.9%) and CD7(28.9%) were expressed in partial patients. Karyotype analysis in 82 patients showed 52.4% (43/82) normal karyotype, 41.5% (34/82) abnormal karyotype, and 6.1% (5/82) failed tests. In the 34 cases with abnormal karyotype, there were 14(41.2%) cases with simple chromosomal abnormality and 20(58.8%) cases with complex karyotype. The positive rate of fusion gene accounted for 16.7% in 60 patients, and the gene mutations accounted for 77.8% in 27 patients. Among 103 cases of AEL, 81 cases were treated with chemotherapy, but 66 cases can be used for therapeutic analysis, as a results the total complete remission rate derived from 2 courses of treatment was 45.5% (30/66). The relapse rate was 36.7% (11/30), and the median relapse time was 15.5 months (6.2-50 months). The median survival time of 66 patients for therapeutic analysis was 29 months. The median survival time of CR patients was very significantly longer than that of the non-CR patients(P=0.001). The 5 year survival rate of CR patients was 65%, the median time of relapse-free survival (RFS) was 46.2 months and 3-years RFS was 58%.

CONCLUSION:

AEL is characterized by the highly expressed CD34 antigen, and complex karyotype. Although AEL has lower CR rate and poor prognosis, CR patients can achieve long-term survival and have good quality of life.

Treatment of Acute Erythroid Leukaemia

The main treatment is similar to that of treating Acute Myeloid Leukaemia (AML). It may include chemotherapy, sometimes along with a targeted therapy drug. This might be followed by a stem cell transplant.

Other drugs (besides standard chemotherapy drugs) may be used to treat people with acute promyelocytic leukaemia (APL).

Surgery and radiation therapy are not major treatments for AML, but they may be used in special circumstances.

Boddu, P., Benton, C.B., Wang, W., Borthakur, G., Khoury, J.D. & Pemmaraju, N. 2018.

"Acute erythroleukemia is a rare form of acute myeloid leukemia recognized by its distinct phenotypic attribute of erythroblastic proliferation. After a century of its descriptive history, many diagnostic, prognostic, and therapeutic implications relating to this unique leukemia subset remain uncertain. The rarity of the disease and the simultaneous involvement of its associated myeloid compartment have complicated in vitro studies of human erythroleukemia cell lines. Although murine and cell line erythroleukemia models have provided valuable insights into pathophysiology, translation of these concepts into treatment are not forthcoming. Integration of knowledge gained through a careful study of these models with more recent data emerging from molecular characterization will help elucidate key mechanistic pathways and provide a much needed framework that accounts for erythroid lineage-specific attributes. "

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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