Epidemiology & Prognostication of Acute Myeloid Leukemia (AML) in India – A Brief Review

ABSTRACT:

AML is represented by aggregation of ≥20% myeloid immature cells in the spongy marrow and most generally raise in the peripheral blood. A cytogenetic finding plays a vital role in the risk management and stratification of AML patients. AML is genetically and functionally a heterogenous malignant disease. In the western world leukemia is one of the most common among all cancers. India ranked 3rd in cancer disease after US and China. Management of AML is challenging specially for medium and low income countries as it causes a huge economic burden to the patient and family. Molecular prognostic biomarkers will help in redefining the risk stratification more efficiently. Targeted drugs in pre-clinical and clinical trial recorded to have promising outcomes in AML.In this review we summarize the prevalence, incidence and prognostication of AML.

KEYWORDS: Acute Myeloid Leukemia (AML), Prognostication, Cytogenetic risk stratification, Clinical features, Risk factor.

INTRODUCTION:

Acute myelogenous leukemia (AML) is a clonal disorder of hematopoietic stem and progenitor cells defined by complex aberrant karyotype due to genetic mutations[1] and epigenetic dysregulation leading to somatic alterations in coding region of genes or in enhancer elements.[2] AML is otherwise

known as acute myeloid leukemia, acute granulocytic leukemia, acute myeloblastic leukemia or acute nonlymphocytic leukemia.[3] AML emanates from the aggregation (through inherited genetic variation , environmental effects, sheer random chance, or some mixture of these) of specific translocations, mutation, and other genetic alterations.[4] The clinic-biological classification of AML includes-morphological, immunophenotypic, cytogenetic and molecular characterization of the leukemia blast cells.

Advanced research in cytogenetics helps us to know the morphology and clinical heterogeneity of AML. On the basis of karyotype, AML has been subdivided into favorable (16% of cases) consisting of inv(16), t(8;21), t(15;17), and t(16;16); intermediate (20% of patients) includes abnormalities which does not come either in favorable or unfavorable karyotypes, and unfavorable (13% of cases) includes add(5q), add(7q), del(5q), del(7q), inv(3), t(3;3), t(6;11), t(9;22), t(10;11), 17p deformities, monosomies 5 or 7, monosomy 17 etc.[5]Molecular genetic investigation of repeated translocations and inversions of chromosomes lead to duplicate genes adjacent to chromosome breakpoint and also to indicate their protein products involved in the leukemogenesis process.[6] The prediction of AML is linked with many determinant; like age, physical status, and presence of an existing disease, subtypes of disease, karyotype, specific gene variation, determining the response to chemotherapy and survival outcome.[7,8] The necessity of AML classification and genetic testing during diagnosis is to risk stratify patients and also to determine appropriate treatment modalities.

EPIDEMIOLOGY OF AML:

In 2001, a worldwide epidemiological study estimated that about 9 million new cancer cases are determined every year and over 4.5 million people died from cancer each year in the world.[9]In 2015 the USA prevalence estimated to be 20,830 new cases of AML (male-12,730 and female-8,100) and an estimated death rate of 10,460 (male-6,110 and female-4,350).[10]

World Health Organization (WHO) reports showed that India has the third highest number of cancer patients in the world after US and China. Among the top 20 cancers affecting the Indian population, leukemia was rated at nine in 2012 by GLOBOCAN. The estimated prevalence was 32, 000 (both men and women) in the country during that period and the death rate was 26,000.Even though India stands 3rd in cancer disease, AML data on prevalence and incidence are sparse. GLOBOCAN estimated the worldwide total leukemia incidence of AML for 2012 to be 351,965 with a 5-year prevalence of 1.5%

and an M: F ratio of 1.4.Incidence rate of AML in India is 3-5 cases/1 lacs. AML accounts for about 15% - 20% of acute leukemia in in children and adolescent & 80% in adult. Incidence of AML rises rapidly after age of 60 median age at diagnosis is 67 years.[11]

A population based study done in different districts of Haryana stated that 51% suffered from acute and 49% from chronic form of AML during 2008-2012.[12]A two year(July 2012 – 2014) prospective study in Christan Medical College, Vellore, southern India reported that there were 380 newly diagnosed AML patients where the median age was 40 years. It was 12.3% in ≤ 15 years of age and 16.3% was≥60 year old.[13] A retrospective (1 year 6 month) and prospective (2 year 7 month) observational studies were done in Hyderabad from October 2007 to December 2011. About103 children were reported with ALL of which 73 (70.87%) were boys and 30 (29.13%) girls with a mean (± SD) age of 4.36 (± 2.66) years, and median of 4 years. Minimum age was 0.4 years and maximum age was 13 years.[14]Arora and Arora in a review summarised the present outcomes of childhood acute lymphoblastic leukemia (ALL) and AML from India. [15] One population-based and the other hospital based studies were included in the review covering time periods being from 1985-2011 for ALL and 1990 -2014 for AML. During this time period, together there were 3761 children with ALL and 336 children with AML. Indian studies of both ALL & AML are exhibited in table 5 & 6 respectively. [**Table 1 & 2 near here]**

Table-1:Studies on ALL from India

S.No	Area	Time period	Number of cases	Age (years)
1	Christian Medical College (CMC), Vellore, southern India[16]	1985-2003	307	Median 6
2	Tata Memorial Hospital (THM), Mumbai, western India[17]	1990-1997	652	Median 7.2
3	All India Institute of Medical Science (AIIMS), New Delhi, northern India[17]	1990-1997	228	Median 7.6
4	Madras metropolitan tumor registry, Chennai, southern India[11]	1990-2001	351	0-14
5	Post Graduate Institute of Medical Education and Research(PGIMER), Chandigarh, northern India[18]	1990-2006	762	Median 5
6	Rajiv Gandhi Cancer Institute, Delhi, northern India[19]	1996-2009	212	Median 6
7	Netaji Subhash Chandra Bose Cancer Research Institute (NSCBCRI), Kolkata, eastern India[20]	2004-2011	500	Median 10
8	Cancer Institute, Chennai, southern India[21]	2005-2011	238	Median 10

Table 2: Studies on AML from India

S.No	Area	Time period	Number of cases	Age (years)
1	Madras metropolitan tumor	1990-2001	60	0-14

	registry, Chennai, southern India[11]			
2	All India Institute of Medical Science (AIIMS), New Delhi, northern India[22]	2000-2011	130	8-18
3	All India Institute of Medical Science (AIIMS), New Delhi, northern India[23]	2005-2009	35	1-18
4	Sri Ganga Ram Hospital (SGRM), northern India[24]	2005-2010	23	Not specified
5	Cancer Institute, Chennai, southern India[25]	2008-2011	65	1-17
6	Christian Medical College (CMC), Vellore, southern India[26]	2012-2014	23	<15

RISK FACTOR FOR DEVELOPMENT OF AML:

- **Older Age Group:** The risk of developing AML will increases from around 60 years older and above age group. It is most commonly occurs in male, when compare to female. The male and female ratio is 11:9.[27]
- **Environmental Risk Factors**: Chemicals exposure- e.g. -Benzenes, insecticides and Hydrocarbons. Ionizing radiation – e.g. –X-rays, CT scan. [28]
- **Lifestyle Risk Factors:** Smoking - There is benzene in cigarette smoke will increase the risk of leukemia.[28]
- **Familial Risk Factors or Genetic Disorders:**Down syndrome, Bloom syndrome, Fanconi anemia, Ataxia telengectesia, Klinefelter syndrome, Blackfan-Diamond syndrome and Neurofibromatosis I. [29]
- **Pre-existing Hematologic Disorder**: Myelodysplastic syndrome (MDS), Aplastic anemia.[29]
- **Chemotherapy or Treatment Associated Risk Factor:**Alkylating agents (deletion chromosome 5 or 7) e.g. - cyclophosphamide. Topoisomerase 2 inhibitor (changes in chromosome long arm 11)e.g. mitoxantrone, etoposide.[30]
- **Auto Immune Disorders Risk Factor:** Rheumatoid arthritis, Auto immune haemolytic anaemia and Ulcerative colitis.[28]

CLINICAL FEATURES OF AML:

Patient with AML usually present with fever, weakness, bleeding tendency (from nose, mouth and rectum etc.,) body pain, cough, weight loss, abdominal pain, pallor, hepatosplenomegaly,

lymphadenopathy and bone marrow failure that causes symptoms of anemia, bleeding from thrombocytopenia, neutropenic infection. Leukostasis and hyper viscosity causing organ dysfunction usually occur with blast cell count > 100000 /ul. Rare but striking manifestation of AML includes Sweet syndrome.[31, 32]

PROGNOSTICATION OF AML:

I. **Prognostic factor –** It mainly relay on both clinical and laboratory based morphology.
   - **Clinical–**based on Age, Secondary AML like Myelodysplastic syndrome (MDS) and Therapy related AML. Patient performance status,extra medullary disease and co- morbidity condition of patients.[33]
   - **Laboratory based –**Investigation like **White Blood Count (**WBC) > 20000/µl at presentation, cytogenetics, molecular genetic deformity, multidrug resistance andCD34 +ve blast.[33]

II. **Prognostic Significance of AML**

The prediction of AML is combined with many determinant; including age, physical status, and presence of an existing disease, subtypes of disease, karyotype, certain gene variations and determining the response to chemotherapy and survival outcome.[34] Genetic marker, *NPM1*gene, is of great significance in copious tumor-combined chromosomal translocations, such as+8, +4, del (9q).[35] *NPM1* is an especially showed phosphoprotein and constantly shuttles between the nucleus and cytoplasm.[36]More freshly, *NPM1* exon 12 variations have been recorded to be ramified in leukemogenesis, and detected in ~35% of AML cases.[37.]

In long-term observation of AML patient it is seen that there is favorable prognostic outcome of patients with biallelic *CEBPA* mutations when compared to monoallele *CEBPA*- mutated CN-AML.[38]Overall survival rate of CN-AML *FLT3-ITD* is shorter when compared with CN-AML wild type *FLT3*.[39]

Core-binding factor leukemias (*RUNX1-RUNX1T1* and *CBFB-myosin11* (*MYH11*)–positive AML) are associated with a favorable prognosis expect when corresponds with *KIT* proto-oncogene receptor tyrosine kinases (*KIT*) mutations which makes a very unfavorable prognosis.[40]The*RUNX1* acts as a primary regulator of hematopoiesis through the regulation of assorted hematopoietic genes, counting those coding for growth factors- Granulocyte-macrophage colony- stimulating factor(GM-CSF), myeloperoxidase (MPO), interleukin 3 (IL3), surface receptors-T-cell receptor alpha and beta chain (TCRA, TCRB,) signaling molecules cyclin dependent kinase inhibitor1A(CDKN1A), BLK proto-oncogene Src family tyrosine kinases (BLK), B-cell lymphoma 2 (BCL2), and transcription activators- signal

transducer and activator of transcription 3 (STAT3), V- Myb Avian Myeloblastosis Viral oncogene homolog (MYB). Thus, *RUNX1*-regulated target genes are crucial for definite hematopoiesis of all lineages.[41]The favorable and unfavorable prognosis markers of the AML is in the table-8 [42]

[Table 3 near here]

Table-3: The Favorable and Unfavorable Prognostics Markers of the AML.

Markers with favorable prognosis	Markers with Unfavorable prognosis
NPM1 mutation	*FLT3* mutation
CEBPA mutation	*MLL-PTD*
	BAALC over expression
	ERG over expression
	EVI1 over expression
	IDH1 mutation
	IDH2 mutation
	ABCG2 over expression
MLL-PTD- Mixed Lineage Leukemia-Partial Tandem Duplications, *BAALC* – Brain and Acute Myeloid Leukemia, Cytoplasmic gene, *ERG* – Erythroblastosis virus E26 oncogene homolog, *EVI1* – Ecotropic virus integration-1 gene, *IDH1* – Isocitrate dehydrogenase 1, *IDH2* - Isocitrate dehydrogenase 2, *ABCG2* – ATP-binding cassette, subfamily G, member 2.	

III. Cytogenetic Risk Stratification of AML:

Currently WHO classification uses a variety of risk stratification factors - good, intermediate, and unfavourable-risk prognosis (Table 4). In general, good prognosis is linked with high term five years survival (LTFY) of up to 65%, intermediate prognosis is combined with LTFY of about 25%, and unfavourable -risk disease is linked with LTFY of less than 10%.[43] AML risk stratification is resolved not only by cytogenetic abnormalities and additionally clarification of certain molecular variations leading to over or below expressions of one or more mitotic or poorly differentiating proteins.[44]**[Table 4 near here]**

Table-4: Cytogenetic Risk Stratification of AML.

S.No	Risk factor	Cytogenetic	Molecular
1	Favorable risk	inv(16), t(16;16), t(8;21), t(15;17) [45]	Normal cytogenetics with: Isolated biallelic *CEBPA* mutation *NPM1* mutation without *FLT3* ITD[46]

2	Intermediate risk	Normal cytogenetics, +8, t (9;11); other chromosomal abnormalities.[47]	*KIT* mutation in core binding factor leukemia: inv (16) or t(16;16) t (8;21)[48]
3	Unfavorable risk	-5, 5q-, -7, 7q-, 11q23 other than t(9;11), inv(3), t(3;3), t(6;9),t(9;22), complex findings (≥3 clonal chromosomal abnormalities) monosomalkarotye with≥ 2 monosomy or one monosomy&≥ 1 additional structural abnormalities.[49,50]	Normal cytogenetics with: *FLT3* ITD.[51]

CONCLUSION:

AML is inherently and effectively a complex cancerousdisease and therefore managing cases of AML is quite challenging. Classification of AML is very important for proper diagnosis and treatment. Two staging systems namely FAB based on morphology and WHO classification regarding chromosome translocation and evidence of dysplasia are very common.WHO has also classified AML into specific cytogenetic and molecular genetics sub-groups. According to NCCN (National Comprehensive Cancer Network) guidelines version 2.2014, AML with frequent translocation (t(8;21)(q22;q22), inv(16)(p13.1q22) or t(16;16)(p13.1;q22) and t(15:17)(q22;q12)) are included in better risk group. Many AML cases show no abnormality on karyotyping, so molecular characterization of CN-AML has become critical diagnostic tool in the management of AML patients. Molecular prognostic biomarker in such clinical situations helps in redefining the risk stratification more efficiently, including targeted therapies.

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