Risk Stratification in Patients of Acute Leukaemia Presenting to a Tertiary Care Hospital in North India

Sangappa Shanker Rao[1], Ajay Sharma[2], Niket Verma[3]

[1]Assistant Professor, Department of General Medicine, Army College of Medical Sciences, Delhi Cantt., New Delhi, India. [2]Professor, Department of Haematology, Army Hospital Research and Referral, New Delhi, India. [3]Assistant Professor, Department of General Medicine, Army College of Medical Sciences, Delhi Cantt., New Delhi, India.

ABSTRACT

BACKGROUND

Clinically and pathologically, leukaemia is subdivided into various groups. The first division is between its acute and chronic forms. This hospital based cross sectional study in a tertiary care armed forces hospital aims at studying the profile of acute leukaemia patients and study the correlation between patient profile and disease prognosis.

METHODS

This observational study included 60 cases of newly diagnosed acute leukaemia presenting between October 2011 to March 2013. All patients underwent routine diagnostic workup for acute leukaemias. Patients were divided into three sub groups – High, Intermediate and Standard risk. Data was analysed after assessing bone marrow response 28 days after starting therapy. Variables such as age, TLC at presentation, immunophenotype, cytogenetics, and extramedullary involvement were taken into account in correlating whether these had any effect on prognosis.

RESULTS

Out of a total of 60 patients, 30 patients had acute myeloid leukaemia and 30 patients had acute lymphoblastic leukaemia. In AML, older patients are more likely to have more comorbidities and have a poorer performance status than younger patients. Extra-medullary infiltrates at diagnosis is associated with poor remission rates and poor overall survival. Outcomes remain poor with extremely high initial WBC counts. Specific secondary chromosome aberrations might affect prognosis of patients. In ALL, 2 out of 6 patients (33%) of high risk (>30 yrs.) achieved remission. High WBC counts at presentation were associated with lower survival. Survival is influenced by immunophenotype: 38% at 3 years for those with the expression of B-lineage antigens compared with 69% for those with T-lineage antigen expression. Patients with high risk cytogenetics were associated with poor outcome even when more intensive therapeutic regimens were used.

CONCLUSIONS

A number of clinical and biological features predict prognosis in AML, but prognosis is also determined by interactions between age, extramedullary disease, leukocyte count at presentation, cytogenetics, and response to therapy etc. In ALL, age, WBC count at presentation and response to therapy have remained strong prognostic indicators of outcome, as have immunophenotypic features and cytogenetics.

KEYWORDS

Risk Factors, Bone Marrow, Leukemia, Myeloid, Acute, Precursor Cell Lymphoblastic Leukemia-Lymphoma

Corresponding Author:
Dr. Niket Verma
Assistant Professor,
Department of General Medicine,
Army College of Medical Sciences,
Delhi Cantt., New Delhi- 110010, India.
E-mail: drniketverma@gmail.com

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BACKGROUND

Leukaemia or leukaemia, from the Greek leukos - white, and haima - blood[1] is a cancer of the blood or bone marrow, characterized by an abnormal increase in the number of white blood cells. It is a broad term covering a spectrum of diseases. In turn, it is part of the even broader group of diseases affecting the blood, bone marrow and lymphoid system, which are all known as haematological neoplasms. About 90% of all leukaemias are diagnosed in adults.[2] most cases of leukaemia occur in older adults, and the median age at diagnosis is 66 years. The most common types of leukaemia in adults are Acute Myelogenous Leukaemia (AML) and Chronic Lymphocytic Leukaemia (CLL). The most common type of leukaemia in children (0 to 19 years old) is Acute Lymphoblastic Leukaemia (ALL). Relative survival rates vary according to a person's age at diagnosis, gender, race and type of leukaemia. The overall five-year relative survival rate for leukaemia has nearly quadrupled in the past 49 years. In India, survival rates of ALL patients vary from 36% to 53%.[3]

Clinically and pathologically, leukaemia is subdivided into a variety of large groups. The first division is between its acute and chronic forms. And as per the cell lines affected into myeloid and lymphoid leukaemias.

- Acute lymphoblastic leukaemia.
- Chronic lymphocytic leukaemia
- Acute myelogenous leukaemia
- Chronic myelogenous leukaemia

Acute myeloid leukaemia (AML), also known as acute myelogenous leukaemia, involves the myeloid line, characterized by the rapid growth of abnormal leukemic cells that accumulate in the bone marrow and interfere with the normal haematopoiesis. AML is the most common acute leukaemia affecting adults, and its incidence increases with age. The incidence of acute myeloid leukaemia (AML) is 3.5 per 100,000 people per year, and the age-adjusted incidence is higher in men than in women (4.3 vs. 2.9). AML incidence increases with age; it is 1.7 in individuals aged <65 years and 15.9 in those aged >65 years.

Acute lymphoblastic leukaemia (ALL) is characterized by excess lymphoblasts and is a neoplastic disease of immature lymphocytes or lymphocyte progenitor cells of either the B- or T-cell lineage.[4] ALL is most common in childhood with a peak incidence at 2-5 years of age, and another peak in old age. The overall cure rate in children is about 80%, and about 45%-60% of adults have long-term disease-free survival.[1]

A number of studies have been done to find out the risk factors & its influence on the prognosis and overall survival of patients suffering from acute leukaemia. However no similar studies have been carried out in Indian setting especially in the armed forces. This hospital based cross sectional study in a tertiary care armed forces hospital aims at studying the profile of acute leukaemia patients and study the correlation between patient profile and disease prognosis.

METHODS

The study was conducted at the Army Hospital (Research & Referral), Delhi Cantt from Oct 2011 to Mar 2013. This observational study included 60 cases of newly diagnosed acute leukaemias in our hospital. All patients underwent routine diagnostic work up for acute leukaemias. The results were then put to statistical analysis to obtain correlation between patient profile and prognosis.

Inclusion Criteria

- Patients suffering from Acute Myeloblastic Leukaemia.
- Patients suffering from Acute Lymphoblastic Leukaemia.

Exclusion Criteria

- Patients suffering from other malignancies along with Acute Leukaemia.

Study Design and Data Collection

This was a hospital based prospective observational study involving 60 patients. Data collection was done by clinical history, examination and investigations. The data collected was subjected to statistical analysis for determining the significance of the results. The following data was collected:

1. Age
2. Initial WBC count
3. Immunophenotype
4. Cytogenetics
   a. Karyotyping
   b. Molecular
5. Extra- medullary involvement
6. Response to initial therapy (Day + 8 for ALL, Day + 14 for AML)

As marrow on Day + 8 (D + 8) and Day + 14 (D + 14) was paucicellular in most patients, response assessment was done by marrow examination on Day + 28 (D + 28) in all cases.

Statistical Analysis

A multi-variate analysis model was used to study the patient profile in acute leukaemia. Risk stratification was done using this model. Patients of AML and ALL were divided into three risk groups - High risk, Intermediate risk and Standard risk as given in Table 1. Data was then put to statistical analysis after assessing bone marrow response on D + 28 in each group. Variables such as age, TLC at presentation, immunophenotype, cytogenetics and extramedullary involvement were taken into account in correlating whether these had any effect on prognosis by student T test and Chi square test.

RESULTS

Out of total 60 patients 30 patients had acute myeloid leukaemia and 30 patients had acute lymphoblastic leukaemia. (Figure 1)

AML –

Sex Distribution

Out of 30 AML Patients 14 patients are Females and 16 patients are males. Out of 14 female patients, 09 achieved Bone marrow remission after chemotherapy and out of 16 male patients 12 achieved remission.

Risk Stratification: Age (Table 2)

(i) Out of 15 patients of standard risk 14 patients achieved remission (93%)
(ii) Out of 10 patients of intermediate risk 07 patients achieved remission (70%)
(iii) Out of 05 high risk patients none achieved remission.

Risk Stratification: Extra Medullary Disease (Table 2)

(i) Out of 19 patients of standard risk, 16 patients achieved remission (84%).
(ii) Out of 11 high risk patients, only 05 achieved remission (45%).

Risk Stratification: Leucocyte Count at Presentation (Table 2)

(i) Out of 24 patients of standard risk 19 achieved remission (79%).
(ii) Out of 04 high risk group 02 achieved remission

Risk Stratification: Cytogenetics (Table 2)

(i) Out of 06 patients with standard risk all achieved remission (100%)
(ii) Out of 14 patients with intermediate risk 11 achieved remission (78.5%)
(iii) Out of 10 high risk only 04 patients achieved remission (40%)

Risk Stratification: Response to Therapy

Out of 30 AML patients 21 patients achieved remission on D + 28 (70%) and 09 patients did not achieve remission (30%). (Figure 2)

ALL

Sex Distribution

(i) Out of 30 patients 14 patients are females and 16 patients are males.
(ii) Out of 14 female patients 11 patients achieved remission.
(iii) Out of 16 male patients 11 achieved remission.

All Subtype

(i) Out of 30 patients of ALL 20 patients are T-cell ALL type and 10 patients are B-cell ALL.

Risk Stratification: Age (Table 2)

(i) Out of 24 patients of standard risk 20 patients achieved remission (83%)
(ii) Out of 06 patients of high risk only 02 achieved remission (33%).

Risk Stratification: Leucocyte Count at Presentation (Table 2)

(i) Out of 17 patients with standard risk (TLC <30000/cumm), 15 patients achieved remission (88%)
(ii) Out of 13 patients with high risk (TLC >30000/cumm) only 07 patients achieved remission (53%).

Risk Stratification: Immunophenotype (Table 2)

(i) Out of 20 patients with standard risk seventeen achieved remission (85%)
(ii) Out of 10 with high risk 05 achieved remission (50%).

Risk Stratification: Cytogenetics (Table 2)

(i) Out of 07 patients of standard risk all achieved remission (100%)
(ii) Out of 18 patients of intermediate risk 15 achieved remission (83%)
(iii) Out of 05 patients of High risk did not achieve remission.

Risk Stratification: Response to Therapy

Out of 30 ALL patients 22 patients achieved remission (73%) and 08 patients did not achieve remission (27%) after induction chemotherapy (D + 28). (Figure 3)

Figure 1. Number and Percentage of Patients with Acute Myeloid Leukaemia and Acute Lymphoblastic Leukaemia

(Out of total 60 patients 30 patients had acute myeloid leukaemia and 30 patients had acute lymphoblastic leukaemia.)

Parameters	Standard Risk	Intermediate Risk	High Risk
Acute Myelogenous Leukaemia			
Age	<45 yrs.		<2 yrs., >60
Initial WBC count	<25000/cumm		>100000/cumm
Extramedullary Disease (Hepatomegaly, splenomegaly, LNE, CNS Disease)	Absent		Present
Cytogenetics	t (15; 17), t (8; 21), inv (16)	Normal Karyotype, del7q, + 8, del9q, abn11q23, + 21, + 22	Abn3q, -5/del (5q), -7, >5 aberrations, complex karyotype
Response to initial Therapy (D + 28)	Remission		Persistent disease
Acute Lymphoblastic Leukaemia			
Age	<30 yrs.		>30 yrs.
Initial WBC count	<30000/cumm		>30000/cumm
Immunophenotype	T-cell ALL		Mature B-cell ALL, early T-cell ALL
Cytogenetics	12p abnormality; t (10; 14) (q24; q11)	Normal; hyperdiploid	Tt9; 22), t (4; 11), t (1; 19), hypodiploid, -7, + 8
Response to initial Therapy(D + 28)	Remission within 04 weeks		Persistent residual disease

Table 1. Classification of Patients into Three Risk Groups - Standard Risk, Intermediate Risk, and High Risk

Risk Group	D + 28 BM (Bone Marrow at day 28)		Total
	Bone Marrow in Remission	Bone Marrow not in Remission	
(I) Acute Myeloid Leukaemia			
Age			
Standard Risk (<45 yrs.)	14	1	15
Intermediate Risk (45-60 yrs.)	7	3	10
High Risk (>60 yrs.)	0	5	5
Total	21	9	30
Extramedullary Disease			
Standard risk (No Organomegaly/LNE)	16	3	19
High risk (Organomegaly/LNE)	5	6	11
Total	21	9	30
Leucocyte Count at Presentation			
Standard Risk (<25000/cumm)	19	5	24
Intermediate Risk (25000-100000/cumm)	0	2	2
High Risk (>100000/cumm)	2	2	4
Total	21	9	30
Cytogenetics			
Standard Risk	6	0	6
Intermediate Risk	11	3	14
High Risk	4	6	10
Total	21	9	30
(II) Acute Lymphoblastic Leukaemia			
Age			
Standard risk (<30 yrs.)	20	4	24
High risk (>30 yrs.)	2	4	6
Total	22	8	30
Leucocyte Count at Presentation			
Standard Risk	15	2	17
High Risk	7	6	13
Total	22	8	30
Immunophenotype			
Standard Risk	17	3	20
High Risk	5	5	10
Total	22	8	30
Cytogenetics			
Standard Risk	7	0	7
Intermediate Risk	15	3	18
High Risk	0	5	5
Total	22	8	30

Table 2. Risk Stratification of Patients with Acute Myeloid Leukaemia (AML) and Acute Lymphoblastic Leukaemia (ALL)

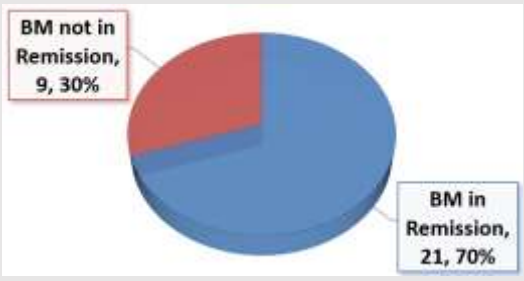

Figure 2. Response to Therapy in Patients with Acute Myelogenous Leukaemia (AML)

(Out of 30 AML patients 21 patients (70%) achieved remission on Day 28 while 9 patients (30%) did not achieve remission).

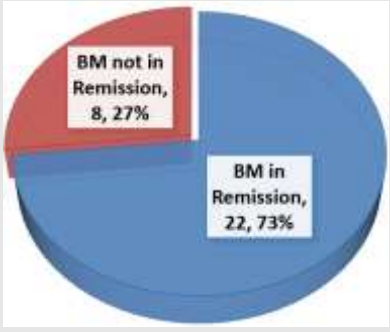

Figure 3. Response to Therapy in Patients with Acute Lymphoblastic Leukaemia (ALL)

(Out of 30 ALL patients 22 patients (73%) achieved remission and 08 patients (27%) did not achieve remission after induction chemotherapy (D + 28)).

DISCUSSION

A number of clinical and biologic features predict prognosis in AML, but prognosis is also determined by interactions between age, extramedullary disease, leukocyte count at presentation, cytogenetics, and response to therapy etc. Many clinical and biological characteristics previously identified as prognostic factors for adult ALL have lost their prognostic value as therapy has evolved and has become more intense. Age, WBC count at presentation and response to therapy have remained strong prognostic indicators of outcome, as have immunophenotypic features and cytogenetics.

This was a hospital based prospective study to stratify patients into various risk groups based on variables like age, TLC at presentation, extramedullary involvement, cytogenetics, IPT, karyotype. The study included 60 consecutive patients with AML and ALL. Response to therapy was assessed by marrow status on D + 28. The following observations were made in each group and will be discussed separately.

Acute Myeloid Leukaemia

1. 14 out of 15 patients (93%) of standard risk (<45 yrs.) and 7 out of 10 patients (70%) of intermediate risk (45-60 yrs.) achieved remission while in the high-risk category (> 60 yrs.) no patient achieved remission (p value <0.001). Both the nature of AML and the health of

the patient change with age. It is axiomatic that older patients are more likely to have more comorbidities and have a poorer performance status than younger patients.[5]

2. In patients with extramedullary disease 16 out of 19 patients of standard risk achieved remission (84%) but only 5 out of 11 patients in high risk category achieved remission (45%) (p value: 0.026). Extra-medullary infiltrates at diagnosis is associated with CD56 expression by leukemic blasts, 11q 23 expression, poor CR rates and poor overall survival.[6]
3. When we consider the TLC of the patients at presentation, 19 out of 24 patients of standard risk (TLC at presentation <25000/cumm) achieved remission (79%). Out of 04 patients in high risk group (TLC at presentation >100000/cumm) 02 achieved remission (p value 0.04). Outcomes remain poor with extremely high initial WBC counts inspite of the supportive care currently available.[7]
4. When we consider Cytogenetics, all 6 patients with standard risk {t (15, 17), t (8, 21), inv (16)} achieved remission (100%) while 11 out of 14 patients with intermediate risk {normal karyotype} achieved remission (78.5%). In the high risk category {Del 7q, Del 5q, complex karyotype}, only 4 out of 10 patients achieved remission (40%) (P value: 0.025). Specific secondary chromosome aberrations, occurring with a frequency too low to be currently tested for outcome, might affect prognosis of patients with t (8; 21), inv (16)/t (16; 16), or t (9; 11). Loss of 5q and 20q bestowed prognosis as poor as that of patients with _5 and del (5q) and with _20 and del (20q), respectively; the outcome of patients with loss of 7q was comparable to the poor outcome of patients with _7.[8]

Acute Lymphoblastic Leukaemia

1. When we consider age of patients, 20 out of 24 patients of standard risk (<30 yrs.) achieved remission (83%) while 2 out of 6 patients of high risk (>30 yrs.) achieved remission (33%) (p value - 0.013). In a study by Larson et al to evaluate a new intensive chemotherapy program for adults with untreated ALL and to examine prospectively the impact of clinical and biologic characteristics on the outcome, 82 of the 87 patients (94%) who were less than 30 years old achieved a clinical remission, compared with 78 of 92 patients (85%) aged between 30 and 59 years and only 7 of 18 patients (39%) aged 60 years and older.[9]
2. When we consider the TLC of the patients at presentation, 15 out of 17 patients with standard risk (TLC <30000/cumm) achieved remission (88%) and 7 out of 13 patients of high risk achieved remission (55%) (p value: 0.034). WBC count were statistically significant with respect to survival (P < .001). Among T-cell or T-Myeloid sub-type ALL patients, the WBC count did not have prognostic significance for survival, but a mediastinal mass was significantly associated with longer survival.[9]
3. Immunophenotypically, 17 out of 20 patients with standard risk (T cell) achieved remission (85%) and 5 out of 10 with high risk (B cell, early T cell) achieved remission (50%) (p value 0.041). Survival is influenced by immunophenotype: 38% at 3 years for those with the expression of B-lineage antigens compared with 69% for those with T-lineage antigen expression.[9]
4. Finally, when we consider cytogenetics, all 7 patients of standard risk (12p abnormality, t (10,14), q24,q11) achieved remission (100%), 15 out of 18 patients of intermediate risk (normal karyotype or hyper diploidy) achieved remission (83%) while none of the 5 patients of High risk {t (9,22), t (4,11), t (1,19), hypodiploidy, -7, + 8} achieved remission(p value: <0.001). Adult patients with ALL with the t (9; 22), t (4; 11), 27, and 18 have a poor outcome even when more intensive therapeutic regimens are used.[10]

CONCLUSIONS

A number of clinical and biological features predict prognosis in AML, but prognosis is also determined by interactions between age, extramedullary disease, leukocyte count at presentation, cytogenetics, and response to therapy etc. In ALL, age, WBC count at presentation and response to therapy have remained strong prognostic indicators of outcome, as have immunophenotypic features and cytogenetics. Therefore, the present study correlates with earlier studies done regarding the various factors that are used in stratifying risk assessment pre-treatment and ultimate outcome in patients with acute leukaemia.

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