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Original Research Article.

A Prospective Study on the Clinical Course of Acute Myeloid Leukemia And Outcomes following the Induction Therapy

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ABSTRACT

Background: Acute myeloid leukemia (AML) is characterized by an increase in the number of myeloid cells in the marrow and an arrest in their maturation, frequently resulting in hematopoietic insufficiency (granulocytopenia, thrombocytopenia, or anemia), with or without leukocytosis. The aim of study is to identify the various modes of presentation and clinical course of different types of acute myeloid leukemia. Another aim is to study the outcomes of the induction therapy and its complications.

Methods: Patients aged more than 12 years with acute myeloid leukemia constituted the study population. These patients were followed up for a period of 6 months after the induction phase. The patients were followed up with clinical evaluation and laboratory investigations during the induction therapy. The various complications arising during this period were carefully evaluated. At the end of induction, patients were evaluated clinically and with investigations including bone marrow examination to look for remission. The data were analyzed with the help of appropriate statistical methods.

Results: Most patients had anemia (96.3%), thrombocytopenia (72%) and an ESR of more than 100mm in the 1st hour (65%). Abnormal peripheral smear is found in all patients and hence this may be a good screening test. AML-M2 (47%) was the commonest type in adults followed by AML-M1 and AML-M3. The induction chemotherapy resulted in a remission rate of 31.3% at the end of induction, the lower rate of remission could be due to increased incidence of infections because most of the patients were in the general ward and the overcrowding might have facilitated hospital-acquired infections. The induction death observed was 68.8% with sepsis being the leading causes of death. All deaths occurred in the first 3 weeks of induction. Infections are fairly common during induction and strict asepsis and meticulous measures are necessary to prevent infection. Patient characteristics such as the age, sex, socioeconomic status, lymphadenopathy, hepatosplenomegaly, and hemogram values did not show any prognostic significance.

Conclusion: The comprehensive knowledge of the clinical presentation could be utilized for making out early diagnosis, which may be of help in treating acute myeloid leukemia and prognosticate the disease outcome.

Keywords: Acute Myeloid Leukemia, Induction Therapy, Outcomes.

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INTRODUCTION

Acute myeloid leukemia (AML) is characterized by an increase in the number of myeloid cells in the marrow and an arrest in their maturation, frequently resulting in hematopoietic insufficiency (granulocytopenia, thrombocytopenia, or anemia), with or without leukocytosis.[1-4]

The incidence of acute myeloid leukemia (AML) is ~3.6 per 100,000 people per year, and the age-adjusted incidence is higher in men than in women (4.4 versus 3.0). AML is a disease of adulthood, with a mean age at diagnosis of 63 years, and the incidence increases with age. AML accounts for approximately 90% of all acute leukemias in adults but for only 13% of leukemia cases in children younger than 10 years of age. The incidence of AML rises rapidly after 50 years of age; the age-specific incidence rates are 3.5/100,000, 15/100,000, and 35/100,000 in persons 50, 70, and 90 years of age, respectively.[5-8]

Genetic predisposition, drug and environmental exposures, and occupational factors have been implicated as possible leukemogenic agents in children and adults. Leukemeogenesis is believed to be a multistep process that requires the susceptibility of a hematopoietic progenitor cell to inductive agents at multiple stages.[9] An increased incidence of acute leukemia has been reported in patients who have received chemotherapy for a

number of malignant and nonmalignant disorders. Most commonly, these secondary t-AMLs occur following the administration of either alkylating agents or topoisomerase II inhibitors.[10-12]

AML is a clonal disorder, with all leukemic cells in a given patient descending from a common progenitor. Studies have demonstrated differing patterns of clonal involvement among patients so that in some (generally younger) patients, only the frankly myeloid leukemic blasts are clonal, whereas in other (often older) patients, normal appearing monocytes, platelets, and red cell precursors might also be of clonal origin. Studies of clonality have also given the surprising result that some patients treated to complete remission with recovery of entirely normal-looking hematopoiesis might still have clonal hematopoiesis, a result consistent with the hypothesis of a multistep pathogenesis for AML.[13-15] The identification of recurrent chromosomal abnormalities—which can include translocations, point mutations, and gene duplications in AML cases—followed by the cloning of many of the involved genes has provided important insights into the pathogenesis of AML. With further investigation, however, it is becoming clear that many of these abnormalities tend to affect a limited number of transcriptional or signal transduction pathways. Of those abnormalities that have been studied extensively, most are pro-oncogenic and are not simply innocent bystanders in the leukemic process.[16-22]

The evolution of new technology in hematopathology has added several new tools for diagnosis, classification, patient management, and determining prognosis of leukemia. The refinements in diagnosis that they provide have set the stage for more specifically directed treatment regimens. Defining the appropriate clinical indications for new techniques, understanding their limitations, and integrating them with existing standard diagnostic methods are all vitally important in realizing their full potential.[23-28] The traditional goal of the treatment of acute myeloid leukemia (AML) is to produce and maintain a complete remission (CR). Criteria for CR are a platelet count higher than 100,000/μL, a neutrophil count higher than 1000/μL, and a bone marrow specimen that has less than 5% blasts.[29-34]

The aim of study is to identify the various modes of presentation and clinical course of different types of acute myeloid leukemia. Another aim is to study the outcomes of the induction therapy and its complications.

MATERIALS AND METHODS

Patients aged more than 12 years with acute myeloid leukemia admitted in a Tertiary care Teaching Institute in North Kerala during a period of one and half years constituted the study population. These patients were followed up for a period of 6 months after the induction phase.

The detailed interview protocol included the clinical features, past illnesses, exposure to radiations or toxic chemicals, residence near high-tension electric lines or coastal areas, dietary habits, addictions etc. A thorough physical examination was done according to the proforma. All patients underwent investigations like CBC, urine routine, peripheral smear and bone marrow examination, chest X-ray, biochemistry investigations and other investigations where indicated.

After confirming the diagnosis of AML, treatment options were planned with the patients. Chemotherapy was given according standard induction regimen, which consists of daunorubicin, 45mg i.v. for three days, and cytarabine, 100mg i.v. by continuous infusion for seven days. Those who were not ready were given palliative chemotherapy of subcutaneous cytarabine.

The patients were followed up with clinical evaluation and laboratory investigations during the induction therapy. The various complications arising during this period were carefully evaluated. At the end of induction, patients were evaluated clinically and with investigations including bone marrow examination to look for remission. The data were analyzed with the help of appropriate statistical methods.

Table 1: Bleeding manifestations.

Type	Number	%
Gum bleed	19	22.9
Skin bleed	9	10.8
GI bleed	7	8.4
Fundal hemorrhage	8	9.6
Intra cranial bleed	3	3.6
Others	8	9.6

Table 2: Organomegaly.

Organ	Number	%
Hepato-splenomegaly	23	27.7
Hepatomegaly	17	20.5
Splenomegaly	6	7.2

Table 3: Hemoglobin values.

Grams / dl	Number	%
Below 5	24	28.9
5 – 8	33	39.8
8.1 – 12	23	27.7
Above 12.1	3	3.6

RESULTS

The patients included in the study were those who were admitted in the wards under Department of Medicine with diagnosis of AML and patients referred from peripheral hospitals with a diagnosis of AML.

Bleeding manifestations were seen in 54 patients (65%). This included bleeding from gums (22.9%), purpura (11%) and from mucosal surfaces. Fundus examination showed hemorrhages in 9.6 % of patients. 3 patients had intra-cerebral bleeding. (Table 1)

Forty patients (48.2%) had enlarged liver. It ranged from 1 cm to 4 cm below the right costal margin in mid-clavicular line. Palpable spleen was seen in 34.9% of patients and ranged from tip of spleen to sizes up to 4 cm. Twenty three patients had both their liver and spleen palpable (27.7%). The hepato-splenomegaly was firm, non-tender and with smooth surface. (Table 2)

The hemoglobin values varied from 2.6 to 13.7 g/dL. Anemia was present in 96.3% of patients. (Table 3)

Total leukocyte count ranged from 500 to 480000 cells / mm^3. Nine patients had counts below 4000 and 84 patients had counts above 10000 cells / mm^3 (TABLE 19). Abnormalities in differential leukocyte count were noticed in 38 patients at the initial evaluation itself (45.8%). (Figure 1)

Figure 1: Total WBC count.

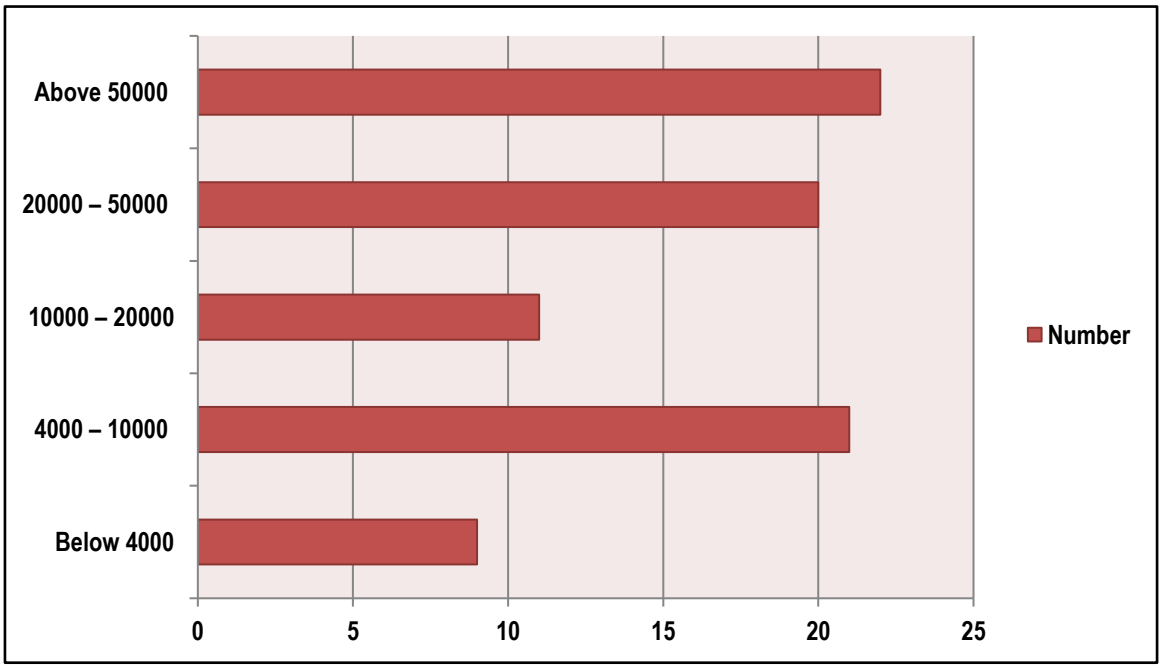

Table 4: Platelet count.

Cells / cu.mm	Number	%
Above 100,000	23	27.7
50,000 – 100,000	9	10.8
20,000 – 50,000	31	37.3
Below 20,000	20	24.1

Table 5: ESR.

mm in 1st hour	Number	%
Below 20	2	2.4
20 -50	5	6.0
50 – 100	21	25.3
100 - 150	37	44.6
Above 150	18	21.7

Table 6: FAB types of AML.

Type	Number	%
M 0	3	3.6
M 1	13	15.7
M 2	39	47.0
M 3	13	15.7
M 4	8	9.6
M 5	4	4.8
M 6	1	1.2
M 7	2	2.4

Table 7: Treatment options

Treatment options	Numbers
Supportive measures only	33
Palliative chemotherapy	19
Induction chemotherapy	16

The range of platelet count was between 2200 to 320000 cells / mm^3 (Table 4) The lowest platelet count was seen in a 13 year old. She presented with bleeding manifestations. The patient who presented initially with deep vein thrombosis of right lower limb had a platelet count of 180000 and a total white cell count of 22000 cells / mm^3.

ESR ranged from 15 to 190 mm in 1st hour. 66.2% % of the patients had ESR of more than 100 mm in 1^{st} hour. (Table 5)

Chest X-ray PA view was taken in most of the patients. Abnormalities in the chest X-ray was observed in 16 patients (19.2%). Peripheral smear was abnormal in all the patients, which included anemia, leukopenia, leukocytosis, thrombocytopenia and abnormal cells suggestive of blasts. The diagnosis of AML was obtained from peripheral blood examination alone in 62 patients (74.7%) and by bone marrow examination and peripheral smear examination together in 68 patients (82%). The bone marrow examination could not be done on all patients. This was because, the general conditions of some of the patients were very poor at the time of presentation and they expired before this could be performed.

The diagnosis of AML was established and the disease classified morphologically by a bone marrow study. The French-American-British system (FAB) classification was employed. (Table 6)

The commonest FAB subtype in adults in our series was AML-M2 (47%) followed by the promyelocytic leukemias (AML-M3) and AML-M1 (15.7% each). AML-M4 accounted for 9.6% of all adult AML. AML-M6 was less common subtype at 1.2%. There were two cases of AML-M7 in our series. Cytogenetics and immunophenotyping were done whenever possible, but most often it was not possible due to technical reasons and financial constraints.

Fifty-two patients (62.7%) had poor general condition at the time of diagnosis with features of pancytopenia and their complications. Only sixty eight patients (82%) opted for treatment. Thirty-three patients (39.8%) opted for supportive care with blood transfusion and antibiotics. Only 16 patients went on for proper induction chemotherapy. Nineteen patients were given palliative

chemotherapy (Table 7). Fifteen patients got discharged at request and were lost in follow up.

General condition of most of the patients was very poor at the time of presentation. Only 16 patients opted for induction chemotherapy. Eight patients expired during chemotherapy. All the patients received cytosine arabinoside and daunorubicin along with supportive measures like blood transfusion and antibiotics. Only six of the patients out of the sixteen could complete the induction phase. All the patients who had undergone induction therapy developed some type of complication. Myelo-suppression was seen in all patients as expected. There was reduction in all the cell lines. Five patients received G-CSF to overcome the severe neutropenia. All patients received transfusions, either Platelet Rich Plasma (PRP) or whole blood during the myelo-suppressed state. Antibiotics were given in patients with fever and prophylactically in patients with severe leukopenia. Eight patients had severe myelo-suppression with features of sepsis and induction was discontinued in five patients. All of them expired within a week despite broad-spectrum antimicrobials and other supportive measures.

Febrile episodes were present during induction in all the patients. Three had pneumonic consolidation, three had intramuscular abscess and one had respiratory infection from which fungal growth was isolated, but he succumbed to the infection despite antifungal therapy. Two of them had diarrheal disease. In rest of them infection could not be attributed to any particular site and blood cultures were negative. Vulvovaginitis occurred in one woman. Seven patients had features of septicemia and received broad-spectrum antimicrobials but 3 of them expired. No organism could be isolated. Two patients developed acute renal failure, which was found to be due to tumor lysis syndrome. One patient died due to intra-cerebral hemorrhage.

Of the six patients who completed induction, chemotherapy only four came for follow up. They subsequently received high dose chemotherapy. But only 2 of them had remission. One of the patients was in remission after 3-maintenance phase, but subsequently had relapsed.

DISCUSSION

Acute Myeloid Leukemia (AML) is the most common malignant disease-affecting adults. It accounts for approximately 80% of acute leukemia in adults. A study by Ghosh S et al[35], adult AML accounted for 76% of all acute leukemias.

The diagnosis of AML was done using peripheral smear and bone marrow examination. In certain cases, trephine biopsy of the bone marrow had to be done. In 74.7% of the cases, diagnosis was obtained from peripheral smear examination alone.

Present study shows that AML-M2 is the commonest type of AML in adults (47%) followed by AML-M3 and AML-M1 (15.7% each). In the series by L. Kumar et al[36] and Ghosh S et al[35] had 38%, 26.4% and 32% respectively. No cases of AML-M7 were observed in all these 3 studies. I the present study, there were two cases of AML-M7. The literature from western population also shows that AML-M2 is the predominant subtype of AML in adults.

Serious life threatening hemorrhage is a common problem in acute leukemia but more common in AML than in ALL. The most prevalent sites of hemorrhage are the skin, eyes and mucous membranes of nose, gingiva and the gastrointestinal tract. The probable mechanisms are thrombocytopenia and platelet dysfunction. The thrombocytopenia may result from marrow infiltration; DIC and infection induced immune thrombocytopenia. Impaired aggregation, deficiency of alpha granules and defective release of Platelet factor–3 contribute to platelet dysfunction. In the present study bleeding manifestations were seen in 65% of patients. Gum bleeding was observed in 22.9%, Skin bleeding was observed in 11%, mucosal bleeds in 27.7% and fundal hemorrhages in 9.6%. Three patients had intracerebral bleed. In the series by Salim et al[37], the incidence of hemorrhagic symptoms was 60%. Study by L. Kumar et al[36] the incidence was 47.5%.

In the present study, hepatomegaly was observed in 48.2% and splenomegaly in 27.7%. Almost similar results were observed in studies by Salim et al[37], L. Kumar et al[36] and Ghosh S et al.[35]

The hemoglobin values varied from 2.6 to 13.7 g/dL. The total leukocyte count ranged from 500 to 480000 cells / mm^3. Platelet count also showed significant variation ranging from 2200 to 320,000 cells / mm^3. ESR ranged from 15 to 190 with a mean value of 114 mm in 1st hour. This value is comparable with previous studies.

After confirming the diagnosis of AML, treatment options were planned with the patients. Chemotherapy was given according standard induction regimen, which consisted of daunorubicin, 45mg i.v. for three days, and cytarabine, 100mg i.v. by continuous infusion for seven days. Those who were not suitable for it given palliative chemotherapy of subcutaneous cytosine arabinoside.

Only 16 patients opted for induction chemotherapy and only six could complete induction chemotherapy. Five patients were in remission at the end of induction. Remission is defined as less than 5% blasts in a cellular marrow, recovery of peripheral neutrophils and platelets and absence of detectable extramedullary leukemia. The remission rate in the present study is 31.3%. Study by L. Kumar et al[36], the remission rate was 60.5%. Induction could not be completed in 5 as they developed severe myelosuppression. There were 11 induction deaths (68.8%). Leading causes of mortality were sepsis in 3 patients, fungal pneumonia in one, tumor lysis syndrome and intracerebral bleed in one each.

Complications during induction chemotherapy were high in this study. This was probably due to lack of isolation of leukaemic patients. Most of the patients who developed infection were getting their regimen from the general wards, where there is overcrowding and thus facilitating hospital acquired infections in neutropenic patients. Several clinical features have been identified to have prognostic significance in AML. These include the total WBC count, hemoglobin concentration, platelet count, cytogenetics abnormalities, etc.

CONCLUSION

1. Most patients had anemia (96.3%), thrombocytopenia (72%) and an ESR of more than 100mm in the 1st hour (65%).
2. Abnormal peripheral smear is found in all patients and hence this may be a good screening test.
3. AML-M2 (47%) was the commonest type in adults followed by AML-M1 and AML-M3.
4. The induction chemotherapy resulted in a remission rate of 31.3% at the end of induction, the lower rate of remission could be due to increased incidence of infections because most of the patients were in the general ward and the

overcrowding might have facilitated hospital-acquired infections.

5. The induction death observed was 68.8% with sepsis being the leading causes of death. All deaths occurred in the first 3 weeks of induction.
6. Infections are fairly common during induction and strict asepsis and meticulous measures are necessary to prevent infection.
7. Patient characteristics such as the age, sex, socioeconomic status, lymphadenopathy, hepatosplenomegaly, and hemogram values did not show any prognostic significance.
8. The need for a separate ward for leukemic patients, were adequate facilities for isolation of neutropenic cases is an obvious requirement.

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