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ORIGINAL ARTICLE

Clinical Profile and Short Term Outcome of Adult Patients with Acute Myeloid Leukemia

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Abstract Acute myeloid leukemia has a poor outcome because of early deaths, high relapse rate and financial constraints. Our hospital provides care free of cost and this study assesses the short term outcome of acute myeloid leukemia in adults. The study was done from September 2013 to May 2015. All patients above 18 years of age were included. Cytarabine infusion 100 mg/m^2 daily for 7 days and Daunorubicin 60 mg/m^2 daily for 3 days was used for induction chemotherapy followed by three cycles of high dose cytarabine as post-remission therapy. One hundred and two patients were included in the study. 48% were males. The median age was 41 years. There was an intention to treat in 84 patients. 13 patients died before chemotherapy and 71 patients (57 non AML M3) received induction chemotherapy. 82% of them had a Eastern Cooperative Oncology Group performance score of ≤ 2. 28 (of 57 non AML M3) patients were alive after post-remission therapy (with 39% deaths during induction phase) and 15 of them were in remission after a median follow up of nine months. The overall event free survival at the end of the study was 22% (16 out of 71). Altogether, 63 out of 84 patients had died. Sepsis was considered as the cause of death in 46% of the patients, but the isolation of causative organism was limited (20%). The treatment outcomes of AML are poor at our centre and the current standard of care needs a significant improvement.

Keywords Acute myeloid leukemia · Resource limited settings · Short term outcome

Introduction

Acute myeloid leukemia (AML) is known to have a poor outcome. The current five year survival rate is 27% in the USA [1]. Steady progress has been made and survival rates are improving, especially in specialist centres where the current five year survival is more than 50% [2]. In India, a relapse free survival of 34% after a median period of follow up of 36 months has been recorded from a referral cancer centre [3]. Poor outcome is because of early deaths and a high relapse rate. Added to this financial constraints are a major problem leading to many patients not receiving adequate treatment. This was up to 70% in another tertiary care referral centre in South India [4]. Our hospital has started providing treatment for AML free of cost. The data from here is expected to provide a truer picture of the outcome and the challenges involved. This study throws light on the clinico-pathological features and short term outcome in adult patients with AML.

Methods

The study was a descriptive study with real time data collection conducted between September 2013 and May 2015. It was approved by the Institute Ethics Committee. All consecutive patients with confirmed diagnosis of AML

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above 18 years of age were included in the study. Written informed consent was obtained from all the participants. AML cases were diagnosed by bone marrow examination and classified based on French–American–British classification system. Cytogenetics and flow cytometry were done from outside labs, if patients could afford it. Outcome information has been provided for all patients and that of non AML M3 patients separately.

Patients were treated according to the existing standard protocols. All treatment was provided free of cost. Patients were mostly managed in Medicine wards in consultation with Medical Oncologist. Isolation beds were provided when available and in their absence patients were managed in general wards. Supportive measures in the form of management of complications of chemotherapy, blood transfusions, treatment of infections and tumor lysis syndrome were undertaken by the treating physicians. Each patient was followed up from the time of diagnosis till the end of the study period. The minimum follow up was for 6 months. Patients' demographic, clinical and laboratory parameters were collected and recorded as per study protocol.

For Induction of non M3 AML, Cytarabine given as a continuous infusion at a dose of 100 mg/m^2 BSA daily for 7 days and Daunorubicin 60 mg/m^2 given daily for 3 days, were used. 3 g/m^2 of Cytarabine given intravenously over three hours every 12 hours on days 1, 3 and 5 was used for post remission chemotherapy for a total of three cycles. All patients received G-CSF injection subcutaneously during the post-remission therapy, starting 24 hours after the last dose of Cytarabine until total leukocyte counts normalized. ATRA (45 mg/m^2 OD) was used for the treatment of APML.

Complete remission was defined as a morphologically leukemia free state with red blood cell transfusion independence, ANC $>$ 1000/μL and platelet count $\geq$ 100,000/μL. Morphologic leukemia free state was defined as $<$ 5% blasts in a bone marrow aspirate sample with marrow spicules and with a count of at least 200 nucleated cells, absence of blasts with Auer rods and absence of extramedullary leukemia [5]. Morphological relapse was defined as reappearance of blasts post-complete remission in the peripheral blood or the bone marrow.

All categorical data were represented as frequencies and percentages. For continuous variables, normality of data was tested. Mean with SD was used for normally distributed data and for non-Gaussian data median with interquartile range was used.

Results

One hundred and two patients were diagnosed with AML between September 2013 and May 2015 and they were included in the study. The median number of hospitalisations per patient was one (IQR 1–3.25) and the median duration of in-hospital stay was 4 weeks (IQR 1.4–12). Forty-nine patients (48%) were males. Patients from Tamil Nadu constituted 85% of the total. The median age of the patients was 41 years (IQR 28–51). Nine patients were more than 60 years old. The baseline characteristics of the patients have been described in Table 1.

Clinical Presentation

Patients had been symptomatic for a median duration of four weeks (IQR − 1–12 weeks) before presentation to the hospital. Most common symptom was fever (87.5%). Fatigue, bleeding manifestations and breathlessness occurred in 20% of the patients. Most common general physical examination finding was conjunctival pallor (95%). No cases of congestive cardiac failure secondary to severe anemia were noted. Ecchymosis and gum hyperplasia were noted in 10% of the patients. Splenomegaly

Table 1 Baseline characteristics of the patients (n = 102)

Characteristic	No. of patients [n (%) or median (IQR)]
Gender	
Male	49 (48.04)
Female	53 (51.96)
Age (years)	41 (28–51)
Place	
Tamil Nadu	87 (85.29)
Pondicherry	10 (9.8)
Others	5
AML (FAB subtype)	
M1	17%
M2	25%
M3	7%
M4	24%
M5	5%
M6	7%
M7	1%
Biphenotypic	14%
ECOG performance score	
1	32%
2	50%
3	18%
4	0%

and sternal tenderness were present in less than 10% of the patients. 96% were anemic with a median Hb of 5.6 g/dL (IQR 4.47–7). Ninety-four percent of the patients had thrombocytopenia at presentation. The median platelet count was 38 × 10^9/L (IQR 18–755). 22.53% had overt bleeding most commonly from the gums. Malena was present in 2% of the patients. Median total leukocyte count was 10.6 × 10^9/L (IQR 4.9–41.73). Median blast percentage at presentation was 59.5% (IQR 39.75–85). Comorbidities were seen in two patients. One had Diabetes and the other patient incidentally detected to be was HBsAg positive.

Diagnosis of Acute Myeloid Leukemia

Of the 102 patients, 64 peripheral smears or bone marrow aspirates were positive for myeloperoxidase stain whereas 48 were sudan black B positive and two were positive for nonspecific esterase. None of them were positive for periodic acid schiff. Flow cytometry was done for 60% of the patients. Cytogenetics and molecular analysis could be done only for 12% of the patients. AML M1, M2 and M4 (17%, 25% and 24% respectively) were common in our study (Table 1). Fourteen patients had morphologically biphenotypic leukemia.

Treatment Details

All the patients were given necessary supportive treatment after admission. Most of the patients needed urgent packed cell or platelet transfusions. 87.5% had presented with history of fever and around 25% of this group was febrile at presentation. No clear focus of infection was found in them. Blood and urine cultures were sterile in most of these patients. Antibiotics (ceftazidime and amikacin) had been started empirically in all of them. Empirical antifungal treatment (Amphotericin B) was given in a case with suspected fungal pneumonia. All patients were routinely screened for features of tumor lysis syndrome.

Of the 102 patients, 18 patients did not receive definitive treatment. Twelve of them were more than 60 years of age, two patients had poor social support and four patients wanted to get treated at a different hospital. Thirteen patients died before induction chemotherapy could be started. Their causes of death were intracerebral bleed (3 patients), hematemesis (1 patient), leukostasis (4 patients), spontaneous tumor lysis with renal failure (4 patients) and sepsis (1 patient).

Chemotherapy

Chemotherapy was initiated in 71 patients. Eighty-two percent of the patients had a ECOG performance score of 1 or 2. Eighteen percent had a score of 3. Seven patients with biphenotypic leukemia received treatment for AML and six of them had died during induction therapy and one remaining patient had a relapse later. Only one patient of seven patients with AML M3 was alive at the end of the study. The survival plot has been shown in Fig. 1. At the end of the study 16 patients (16%) were having an event free survival. The overall summary of the induction chemotherapy and post chemotherapy phase has been

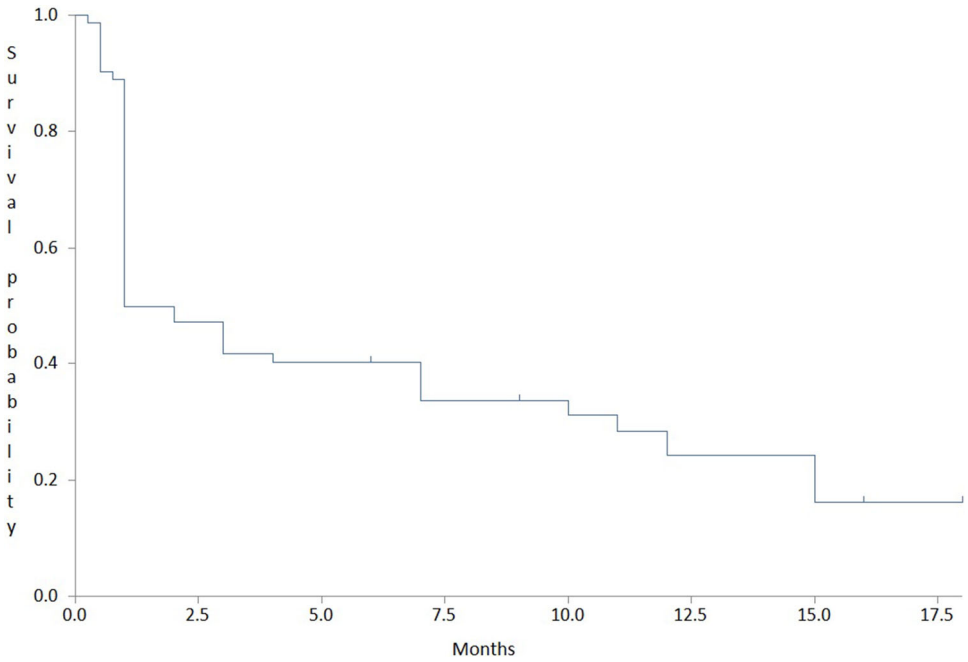

Fig. 1 Kaplan Meier survival plot (n = 84)

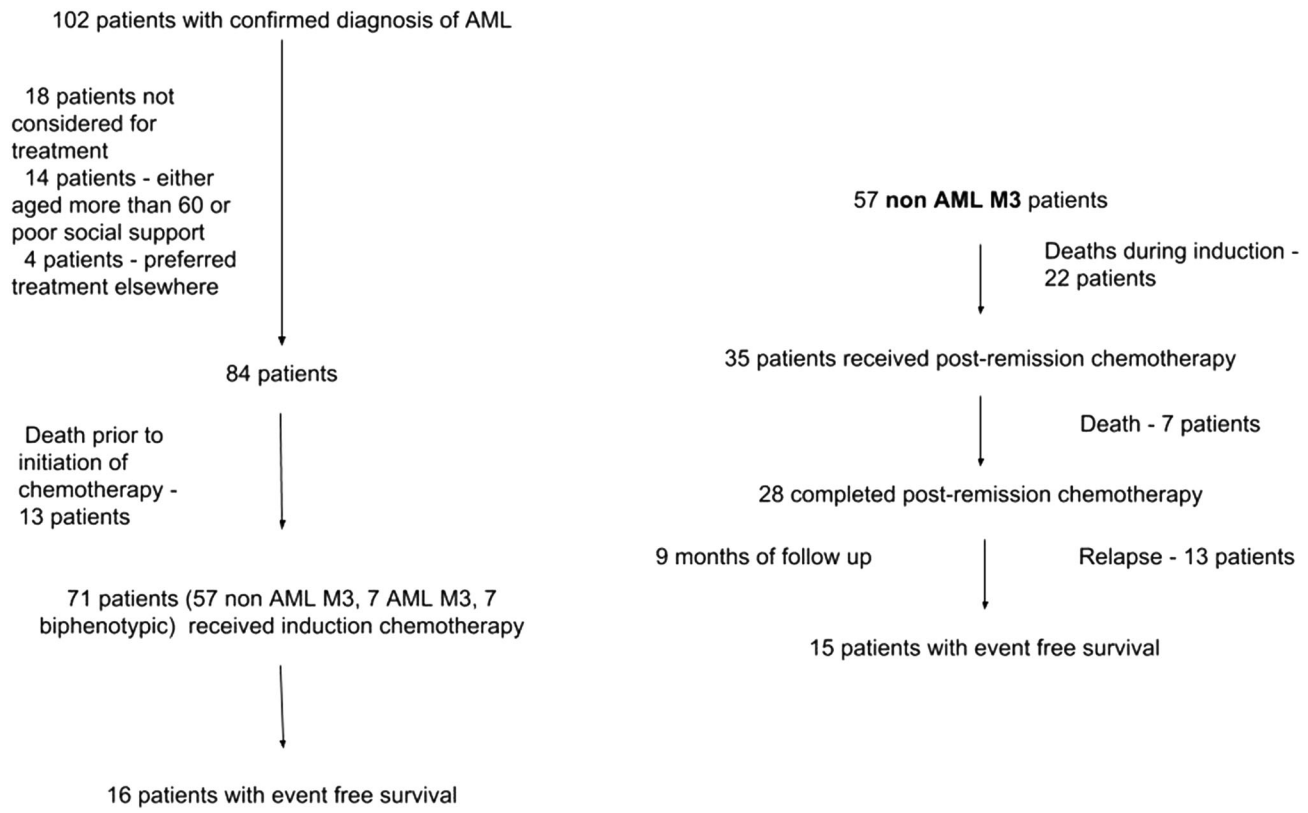

Fig. 2 Flow chart depicting loss of patients at each phase of therapy

provided in Fig. 2. The treatment details for patients with Non AML M3 after excluding biphenotypic leukemia (57 patients) is provided below.

Induction Phase

Of the 57 patients who received induction chemotherapy, 35 patients achieved complete remission. Three patients needed re-induction therapy. 22 patients (39%) died during this phase. Twenty patients died of sepsis (3 fungal pneumonia, 1 neutropenic colitis, 16 sepsis without focus). One patient had fatal intracerebral bleeding and one patient died of renal failure. None of the patients developed Cytarabine induced cerebellar toxicity.

The association of certain clinical parameters with the death of patients during induction therapy was assessed (Table 2). Duration of symptoms prior to diagnosis, age of the patient, baseline white blood cell count, baseline platelet count and the performance status of the patients, were not different between the patients who died and the patients who achieved remission. The peripheral blood blast percentage was higher in the patients who died during induction phase ($P = 0.052$).

Table 2 Association of certain clinical parameters with deaths during induction chemotherapy in patients with non AML M3 (N = 57)

Clinical parameter	Patients who died during induction phase (N = 22)	Patients who achieved remission (N = 35)	*P* value
Average duration of symptom onset to diagnosis (in days)	28	26	$P = 0.78$
Average age in years	35	36.5	$P = 0.67$
Average baseline WBC count (per cmm)	46,222	31,523	$P = 0.36$
Average peripheral blood blast percentage	62.3	49.6	$P = 0.052$
Average platelet count at baseline (per cmm)	49,811	47,066	$P = 0.8$
ECOG score $\geq$ 3 at baseline	4	7	$P = 0.88$

Post-Remission Therapy

All the 37 patients who achieved complete remission received post-remission chemotherapy. Seven of them died during the consolidation phase. Six patients died due to sepsis (fungal pneumonia-1, neutropenic colitis-1, sepsis without focus-4) and one died of intracerebral bleed. One patient developed cerebellar cytotoxicity after the first cycle of HiDAC and he underwent autologous stem cell transplantation.

Relapse

Thirty patients who completed consolidation chemotherapy were followed up for a median duration of 9 months. Fourteen (46%) of them relapsed (including the patient who underwent autologous stem cell transplantation) within a median of 6 months (IQR – 3–9 months). Nine out of these 14 patients died by the time the study ended. Sixteen patients (22%) were alive and in remission at the end of the study. They had been followed up for a median of nine months and they were free of any events.

Summary of Mortality Data

Altogether, 63 out of 84 patients in whom there was an intention to treat had died. Mortality was more than 70% in any FAB subtype including AML M3 (85%). Thirteen (21%) patients died before initiation of induction chemotherapy, 34 (54%) died during the induction phase, 7 (11%) patients died during consolidation phase and 9 (14%) patients died later due to relapse. Sepsis was considered as the cause of death in nearly 46% of the patients, but the isolation of causative organism was limited (20%). Five patients died of fungal sepsis. One patient had candidal bacteremia. In four patients, where chest X-rays had shown diffuse bilateral infiltrates, Aspergillus species was isolated from the post-mortem lung biopsies.

Discussion

In this study, data has been gathered regarding clinical presentation, diagnosis, management and short term outcome in patients with AML at our hospital. The overall survival was 22% in the patients who received chemotherapy after an average period of 4.4 months.

The median age at diagnosis was 41 years. This is substantially less than that reported in the USA (68 years) [1], but comparable to another study from a tertiary hospital in South India [4]. There is no information available as to the cause of this. FAB subtypes M2 and M4 were the most common subtypes similar to the studies from other tertiary care centres [4, 6]. The diagnosis relied mostly on morphological methods. At the time of writing the paper flow cytometry has been made available in the hospital and cytogenetic studies are being outsourced.

Induction regimen used was the standard '7 + 3' regimen. The dose of daunorubicin was 60 mg/m^2, similar to the dose in study by Philip et al. [4]. Thirty-nine percent of the patients died during the induction phase. This is higher when compared to other reports from India, 25% and 30% at Christian Medical College, Vellore and Tata Memorial Hospital, Mumbai respectively [3, 4]. In Tertiary centres in Europe it is less than 10% [2]. The ECOG score at presentation, which is a predictor of early death was 2 or less in 82% of the patients [7]. Sepsis accounted for nearly 50% of the deaths. Causative organism could not be isolated in most patients. The patients had been managed in routine medical wards without proper isolation facilities. Even for selected patients treated at a better tertiary care facility in South India, the initial mortality was more than double seen in the West (24.7% vs. 10%) [4, 7]. It can be pondered whether the dose of daunorubicin being used is more toxic to our patients.

Fourty-six percent of the patients had experienced a relapse during a median period of follow up of 9 months. A 44% relapse rate has been reported from Tata Memorial Hospital, Mumbai but their follow up period was much longer (36 months) [3]. Our relapse rates are expected to be higher because patients with any risk profile received the same consolidation therapy and there is limited access to allogeneic transplantation.

Moving forward, better diagnostic modalities need to be made available, patients need to be treated in proper isolation wards and allogeneic transplant facility needs to be created. Population based cancer registries need to be maintained so that proper outcome data become available. The National Centre for Disease Informatics and Research, India is making efforts in this direction.

In conclusion, the treatment outcomes of AML are poor at our centre and plenty of work needs to be done both in improving the current standards of care and in adopting newer treatment modalities.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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