ORIGINAL ARTICLE

ONE YEAR DISEASE FREE SURVIVAL IN ACUTE MYELOID LEUKEMIA PATIENTS AFTER INDUCTION REMISSION

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Background: Diagnostic karyotyping analysis is routinely used in acute myeloid leukaemia (AML) clinics. Categorization of patients into risk stratified groups (favourable, intermediate and unfavourable) according to cytogenetic findings can serve as a valuable independent prognostic factor. The aim of this study was to assess the one-year disease free survival rate in AML patients after induction remission presenting at tertiary care hospital of Karachi. **Methods:** It was a longitudinal study conducted at the department of Medical oncology of Jinnah Postgraduate Medical Center, Karachi from Jun 2017–Jan 2019. Ninety-three diagnosed cases of AML of age 15-55 years of either gender were included in the study. All patients received the first cycle of "3+7" regime for induction chemotherapy. This includes Daunorubicin 45 mg/m^2 on days 1 to 3 and Cytarabine in a dose of 100 mg/m^2 from day 1–7. Marrow response was assessed on the 21th day of induction therapy. If the bone marrow includes lesser than five percent blast cells then it was labelled as complete remission (CR). The patients who achieved CR and normal haematopoiesis were eligible to receive 4 cycles of consolidation therapy with cytarabine 3 mg/m^2 every 12 hour on days 1, 3 and 5. Consolidation cycles were monthly administered. All the patients who achieved CR were follow up for the duration of one year for disease free survival. On follow up monthly visits, outcomes were assessed using CBC report and physical examination. **Results:** After 1 year, out of 72 AML patients, 19 patients remained in complete remission, 5 patients lost to follow up, 3 relapses, 19 showed persistent disease & 28 died during consolidation. According to cytogenetic status, CR was achieved in 6 patients (50%) with favourable cytogenetic, 14 patients (28%) with intermediate cytogenetic and 2 patients (20%) with unfavourable cytogenetic status. The highest median survival time was observed in patients with favourable cytogenetic status as 5.23 months. However, there was no significant difference was observed in survival time with respect to cytogenetic status. **Conclusion:** The "3+7" regime of Daunorubicin & Cytarabine is effective in inducing induction remission and increases 1 year survival, however chemotherapy related morality rate was high in unfavourable cytogenetic group.
Keywords: Survival rate; Remission; AML, Induction chemotherapy; Cytogenetic; Poor prognosis

Citation: Shaikh MR, Haider G, Shahid A, Rahool R, Beg S, Memon P, Bhunisha, Nouman M. One year disease free survival in acute myeloid leukaemia patients after induction remission. J Ayub Med Coll Abbottabad 2021;33(3):475–9.

INTRODUCTION

Acute myeloid leukaemia (AML) is a rare clonal hematopoietic disease, genetically heterogeneous and classified by abnormal increase of myeloid blast cells in the peripheral blood and bone marrow resulting complications such as infection, bleeding and organ infiltration.[1–3] In year 2019, 21,450 new cases of AML diagnosed and 10,920 individuals die due to it in US.[4] Acute myeloid leukaemia is the disease of elder age group and rare under the age of 45. AML is mostly common in males than females, but average lifetime odds of having AML is half of 1% in both genders. In Pakistan AML is a rare disease and a study of 62 patients reported AML in 16% of all the leukaemia's cases from Pakistan and it is frequent among adults (64%) and male gender (57%).[5,6] The main aim of the AML therapy is to achieve or maintain complete remission (CR), meaning that the number of blood cells is normal, bone marrow contains <5% blast cell counts.[7] The likelihood of recurrence of AML sharply decreases to less than ten percent after three years in CR.[8] Over the previous 30 years, AML treatment has been split into 2 stages: 1) remission induction therapy and 2) post remission therapy.[9,10] Acute myeloid leukaemia treatment usually involves at least one intensive induction chemotherapy course followed by intensive consolidation.[1,11] Up to 80% of AML patients achieve complete remission after first cycle of induction therapy, however 50% of them experience relapse in 5 year.[12] The probability of achieving CR mainly depends on particular prognostic factors including clinical, cytogenetic and molecular markers.[7,13] The relapse can also be treated with repeat induction. Hence the chances of achieving complete remission after re-induction and disease free interval decreases.[14] In a study conducted at AKUH seventy four AML patients were enrolled out of which 29% died during induction therapy and 65.4% achieved complete remission.[15] According to American Cancer Society's (ACS), the 5-year survival rate for AML patient of age 20 or more is approximately 24% and younger AML patients (<20 years), the survival rate is 67%.[16] In another research, the overall survival and event-free survival for the 50 AML patients after first relapse

were 29% and 19% at 70 months, respectively.[17] Hence, the aim of this study was to assess the one year disease free survival rate in AML patients after induction remission presenting at tertiary care hospital of Karachi. Pakistani literature is scarce in this regard. This study would be helpful in improving management, treatment and survival rate of AML patients.

MATERIAL AND METHODS

It was a longitudinal study conducted at the department of Medical oncology of Jinnah Postgraduate Medical Center, Karachi from Jun 2017– Jan 2019. Sample size was estimated as 93 by using Open Epi sample size calculator taking statistics for complete remission as 65.4%, margin of error as 9.7% and 95% confidence level.[10] The non-probability consecutive sampling technique was employed. All the diagnosed cases of AML of age 15–55 years of either gender were included in the study. Patients who were on consolidation and relapsed on consolidation were excluded from the study.

The approval from ethical review committee was sought before conducting study. Informed written and verbal consent was taken from all the eligible patients. Information regarding socio-demographic & clinical factors were obtained from all the patients and noted on pre-designed *proforma*. The diagnosis of cytogenetic abnormality was done on bone marrow biopsy sample only. The cytogenetic abnormalities were classified according to WHO 2016 update; the three cytogenetic risk groups were defined as favourable, intermediate and unfavourable.[18] The favourable cytogenetic risk group consist t (15;17), t (8;21) or t (16;16) or inv (16), the unfavourable cytogenetic risk group consist inv (3), t(9;22), 7q- & 5q- and complex karyotype and the intermediate cytogenetic risk group consist del (9q), del (20q), t (9;11), del (7q), -Y, +8, +11, +13, and +21 or normal karyotype. All patients have received the first cycle of "3+7" regime for induction chemotherapy. This includes Daunorubicin 45 mg/m^2 on days 1 to 3 and Cytarabine in a dose of 100 mg/m^2 from day 1–7. Marrow response was assessed on the 21st day of induction therapy (Due to lack of resources, financial issues and unstable patients we have done late bone marrow assessment on 21st day). If the bone marrow includes lesser than five percent blast cells then it was labelled as CR. The patients who achieved CR in normal CBC and peripheral blood film documented were deemed eligible for subsequent consolidation cycle at cytarabine 3 mg/m^2 every 12 hour on days 1, 3 and 5. Consolidation cycles were monthly administered. All the patients who achieved CR were follow up for the duration of one year for disease free survival. On follow up monthly visits, outcomes were assessed using CBC report and physical examination. All the data were analysed through SPSS version 23. Baseline characteristics were presented as Mean±SD and frequency (%). The median survival time was calculated with respect to cytogenetic status. Cox-proportional-hazard regression model was used to identify the significance of cytogenetic status on prognosis. The hazard ratios were calculated along with 95% confidence intervals (CI). Kaplan Meier and time to event plot were used to investigate all patients who were on follow-up for 1 year from admission. *p*-value less and equal to 0.05 will be taken as statistically significant.

RESULTS

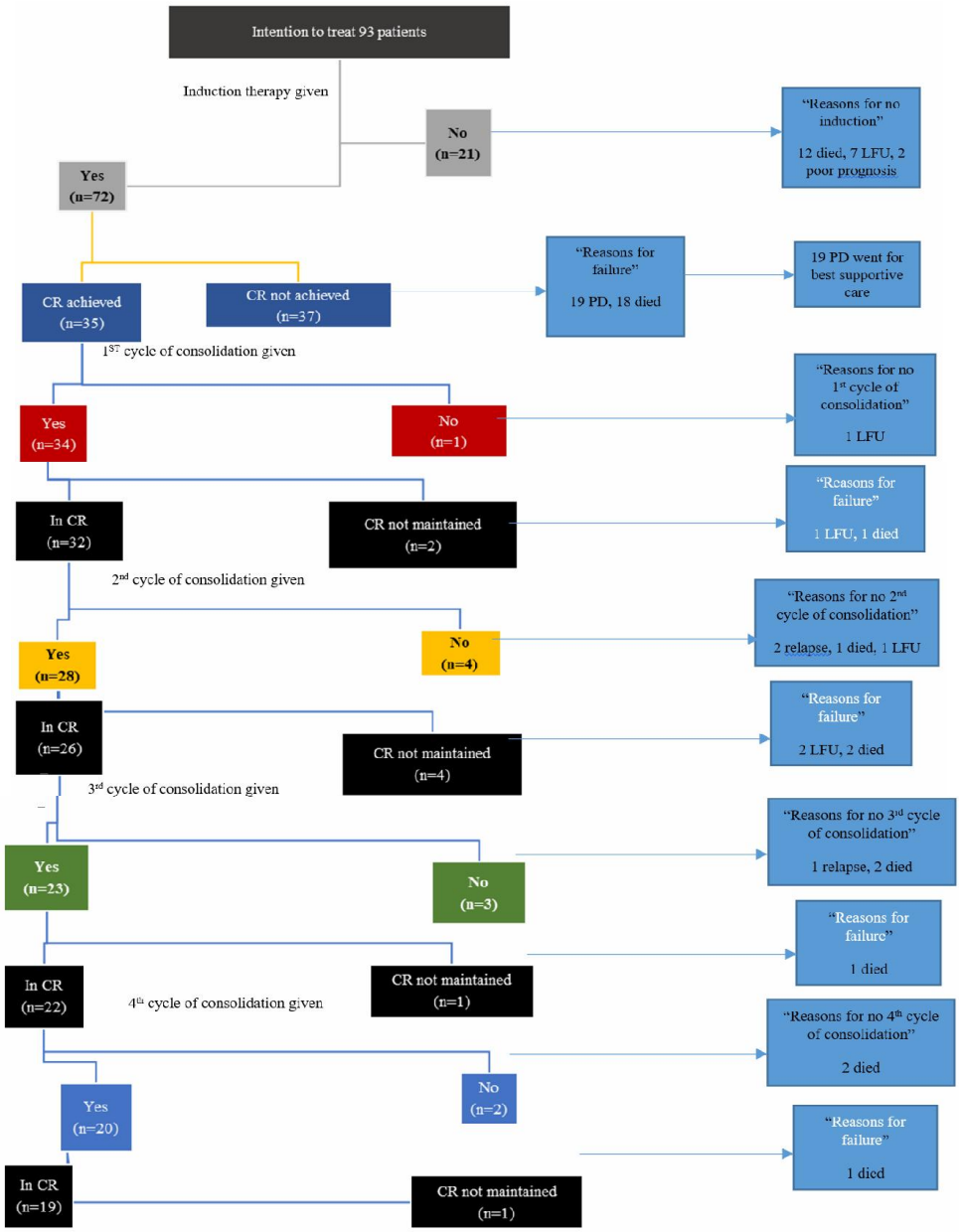
Total ninety-three patients of AML were included. The mean age (years), platelets count (X10^9), WBC(X10^9) & Hb level (g/dl) of the patients were reported as 32.16±11.81, 49.46±66.85, 32.29±49.26 & 9.31±8.10 respectively. About 49.5% of the AML patients were males and 50.5% were females. Most of the patients were in intermediate risk group (67.7%), followed by favourable (17.2%) and unfavourable risk group (15.1%). (Table-1) In figure 1, the results showed that 72 (77.4%) patients received induction therapy and among them 35 patients (48.6%) achieved complete remission (CR). Post CR, 34 patients underwent for 1st cycle of consolidation therapy wherein 28 patients underwent for 2nd cycle of consolidation therapy, 23 patients maintained till 3rd cycle of consolidation therapy and lastly 20 patients underwent for 4th cycle of consolidation therapy. After 1 year, out of 72 AML patients, 19 patients remained in complete remission, 5 patients lost to follow up, 3 relapses, 19 showed persistent disease & 28 died during consolidation.

According to cytogenetic status, CR was achieved in 6 patients (50%) with favourable cytogenetic, 14 patients (28%) with intermediate cytogenetic and 2 patients (20%) with unfavourable cytogenetic status. The highest median survival time was observed in patients with favourable cytogenetic status as 5.23 (4.88–5.58) months. However, there was no significant difference was observed in survival time with respect to cytogenetic status. Whereas the treatment related mortality was 6.01 times higher among unfavourable cytogenetic status as compared to favourable cytogenetic status (Table-2).

The probability of remaining in remission after induction & consolidation therapy among favourable cytogenetic status was estimated as 16.7% at 5 to 5.3 months, 13.7% for intermediate cytogenetic status at 3.5 to 5.6 months and 50% for 3.9 to 4.3 months for unfavourable cytogenetic status. (Figure-2)

Table-1: Baseline characteristics of AML patients (n=93)

Quantitative Variables	**Mean**	**SD**
Age (years)	32.16	11.81
Platelets ($X10^9$)	49.46	66.85
WBC ($X10^9$)	32.29	49.26
Hb level (g/dl)	9.31	8.10
Qualitative variables	**n**	%
Male	46	49.5
Female	47	50.5
Cytogenetic status		
Favourable	16	17.2
Intermediate	63	67.7
Unfavourable	14	15.1



*PD=Persistent disease, LFU= Lost to follow up, CR= Complete remission

Figure-1: Complete remission after induction and consolidation therapy

Table-2: Stratification of CR with respect to cytogenetic status

Cytogenetic Status	CR	Median survival time (months) (95% CI)	HR (95% CI)	*p*-value
Favourable (n=12)	6	5.23 (4.88–5.58)	1	0.09
Intermediate (n=50)	14	4.73 (4.29–5.17)	1.58 (0.59–4.23)	
Unfavourable (n=10)	2	3.93 (3.75–4.47)	6.01 (1.01–35.54)	

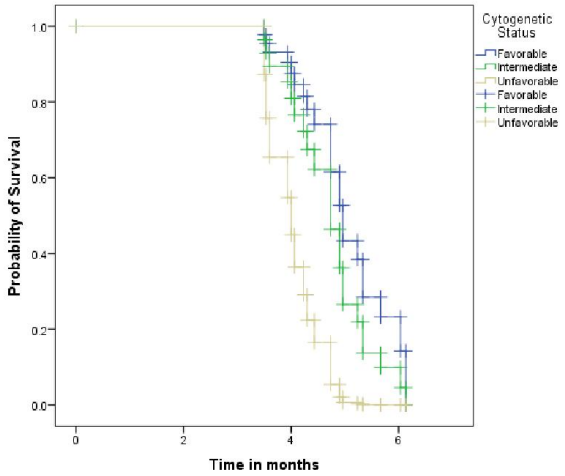


Figure-2: Probability of survival among cytogenetic risk groups

DISCUSSION

Traditionally, management of AML patients is very challenging. The main goal in AML patient is to increase their life expectancy. In order to measure survival time in AML patients, induction therapy with complete remission followed by consolidation therapy is conventional. The management of AML patients is still debatable. However, the major priority in these patients is to enhance survival time and clear blast cells from the blood as much as possible. The overall blood count is great prognostic factor in AML patients. The cancer of blood appears to be highly fatal and hence survival rate can be calculated to increase patient's life.

The current study demonstrates that about 49.5% of the AML patients were males and 50.5% were females. Most of the patients were in intermediate risk group (67.7%), followed by favourable (17.2%) and unfavourable risk group (15.1%). And the overall survival time out of 1 year was 6 months. Contrary to a study using Kaplan-Meir method, the 12 weeks survival time of AML patients was measured. The patients were divided into 4 groups from the start of induction therapy till complete remission. The patients had no correlation between overall survival and event free progression.[19]

According to the present study, the overall survival time was 6 months. Seventy-two patients had received the first cycle of Daunorubicin 45mg/m^2 on days 1–3 and Cytarabine in a dose of 100 mg/m^2 from day 1–7 for induction chemotherapy. Post first therapy of induction, patients who had showed complete remission had received 4 cycles of consolidation therapy with cytarabine 3 mg/m^2 every 12 hour on days 1, 3 and 5. Whereas in the other study almost 50% had complete remission with standard regimen.[20] The results of the present study also emphasized high mortality rate related to AML. The AML diagnosis is highly dependent upon white cell count, the cytogenetic risk group and multi drug resistance status of the patients.[21] All these factors lead to challenging treatment which is explainable from the results of current study. There were 12 fatalities pre-induction and 2 patients were not able to receive 1st cycle of induction dose due to poor outcomes.[21]

The cytogenetic status is highly linked with prognosis of AML. In the present study, the calculated hazard ratio of unfavourable cytogenetic group is 6.01 (1.01–35.54) which explicates less survival time and poor treatment outcomes. Similarly, in a study by Hu J CY *et al*. had a greater number of patients having unfavourable cytogenetic status. The study compared 2 drug regimens in which standard induction therapy which is also used in the present study (daunorubicin & cytarabine) was found effective than low intensity induction therapy. However, in contrast to low intensity regimen, the patients who had greater complications and overall performance was poor had successful outcomes for low dose induction therapy.[20] The present study showed after 1 year, out of 72 AML patients who underwent induction therapy, 26.3% patients remained in complete remission, unfortunately 4.16% patients showed relapse and 38.8% patient died during one year period. The results showed similar findings comparable to Gerstung *et al* study, however, he registered intermediate risk group AML patients in his study.[22]

Within the limitation of this study, it is recommended to follow up for at least 5 years to assess outcomes of induction chemotherapy, consolidation and evaluating therapeutic outcomes. Hence randomize control trials are recommended for accurate knowledge regarding survival.

CONCLUSION

Induction chemotherapy treatment is effective and globally known treatment for AML cases. The "3+7" regime of Daunorubicin & Cytarabine is efficacious in increasing survival rate. In addition, as a part of

treatment plan consolidation therapy is important predictor for recurrence of the cancer. However, with the poor prognosis of acute Myeloid Leukemia, morality rate was still noticeable. The survival analysis in these patients require accurate information from large sample sizes. Generally tailored treatment decisions and initiating induction therapy could lessen the mortality rate in the patients with AML.

AUTHORS' CONTRIBUTION

MRS: Conceptualization of study design. Data collection, data analysis, write-up, proof reading.GH: Write-up, proof reading. All other authors contributed equally.

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Submitted: November 18, 2019	*Revised: January 18, 2020*	*Accepted: January 27,2020*

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