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ORIGINAL ARTICLE

Induction mortality and remission rate after 1st cycle of standard 7+3 regimen chemotherapy in patients of acute myeloid leukemia.

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ABSTRACT… Objective: To determine the remission rate, mortality rate, and induction failure after standard 7+3 induction chemotherapy in patients with AML in Pakistan. **Study Design:** This study utilized a descriptive design. **Setting:** The study was conducted at the National Institute of Blood and Marrow Transplant Rawalpindi (NIBMT/AFBMTC). **Period:** August 2018 to May 2021. **Methods:** The study cohort comprised 88 patients aged 15 to 55 years, inclusive of both genders, diagnosed with acute myeloid leukemia (AML). All participants received standard induction chemotherapy. Remission status was evaluated either upon hematologic recovery or on Day 42 of treatment, whichever occurred first. Patients who died prior to initiating induction chemotherapy or discontinued hospitalization before completing the induction course were excluded from the analysis. Written informed consent was obtained from each enrolled patient. **Results:** A total of 88 patients were enrolled, with a mean age of 29.18±10.6 years. Sixty-one percent of the patients were 30 years or younger, while the remaining 38.6% were aged between 31 and 55 years. Among the patients, 50 (57%) were male and 38 (43%) were female, resulting in a male-to-female ratio of 1:1.3. The mean blast percentage in the diagnostic bone marrow was 75±21.9%. The majority of patients belonged to the AML M2 subtype (50%), followed by AML M4 (15.9%), AML M1 (13.6%), and AML M0, M5, and AML-MRC (6.8% each). Remission was achieved in 71.6% of the total patients, while 4.5% were not assessed for remission due to death, and 23.9% were refractory to the first cycle of chemotherapy. The frequency of induction mortality in our study was 4.5%. **Conclusion:** The 7+3 regimen is an effective intensive induction chemotherapy for fit patients to achieve remission with an acceptable treatment-related mortality rate.

Key words: Acute Myeloid Leukemia, Induction Mortality, Remission Rate, Induction Chemotherapy, 7+3 Chemotherapy.

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INTRODUCTION

Acute Myeloid Leukemia (AML) is a clonal proliferative malignancy of the myeloid lineage, marked by the infiltration of the bone marrow, peripheral blood, and extramedullary sites by poorly differentiated blast cells. Historically considered incurable five decades ago, AML treatment has undergone transformative advancements, leading to cure rates of approximately 35–40% among adults under 60 years of age, and between 5% to 15% in individuals aged above 60. However, outcomes remain dismal for elderly patients who are ineligible for intensive chemotherapy, with median survival ranging from 5 to 10 months.[1] The median age at diagnosis in Western populations is reported to be around 70 years, with a strong correlation observed between increasing age and AML incidence.[2,3] Annually, AML is diagnosed in approximately 2 to 3 children per 100,000, compared to around 15 cases per 100,000 adults.[4]

Management of acute myeloid leukemia (AML) is traditionally structured into two main phases: induction and consolidation. The induction phase involves administering intensive combination chemotherapy with the primary goal of attaining complete remission (CR) by swiftly decreasing the leukemic cell load and promoting the restoration of normal bone marrow function.

A commonly employed induction protocol consists of a continuous seven-day infusion of cytarabine alongside a three-day course of anthracycline, commonly recognized as the "7+3" regimen.[5,6]

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In young adults, the CR rate with standard induction therapy ranges from 60% to 80%. However, older age groups have lower CR rates with intensive chemotherapies.[7]

Historically, there has been significant treatment-related mortality (TRM) associated with chemotherapy, particularly in older age groups and patients with poor performance status.[8] However, over the past several decades, treatment-related mortality (TRM) has declined markedly, reflecting advancements in supportive care, patient stratification, and therapeutic protocols. For instance, TRM decreased from 18% in South West Oncology Group (SWOG) trials and 16% at MD Anderson (MDA) during the 1991–1995 period, dropping to 3% at SWOG and 4% at MDA by 2006-2009.[9]

A multi-center study conducted in India reported a CR rate of 52.8% and induction mortality ranging from 6.1% to 43% across different centers.[10] Similarly, a single-center study in India showed a CR rate of 70% and an induction mortality rate of 18.4%.[11] However, there is currently no recent similar study available from Pakistan. A single-center study conducted in 1996 in Pakistan reported a CR rate of 65% and an induction mortality rate of 29%.[12]

Given the lack of recent data from Pakistan and the evolving landscape of AML treatment, it is essential to investigate the outcomes of induction therapy, including CR rates and induction mortality, in AML patients in the Pakistani population. Therefore, the aim of this study is to evaluate the efficacy and safety of standard induction chemotherapy in patients with AML in Pakistan, providing valuable insights into the current landscape of AML treatment outcomes in this region.

METHODS

This descriptive study was carried out at the Armed Forces Bone Marrow Transplant Centre in Rawalpindi over a period spanning August 2018 to May 2021. Patients aged 15 to 55 years of both genders, diagnosed with AML and undergoing induction chemotherapy, were included. The cohort was stratified into two age groups: 15–30 years and 31–55 years. Due to resource limitations, germline mutation testing was not performed. Patients with therapy-related AML, acute promyelocytic leukemia (APL), those deemed unfit for chemotherapy, and individuals who did not provide informed consent were excluded. Institutional ethical approval was obtained from the Hospital's Ethical Review Committee on 20th February 2019.

Baseline data included complete blood count, blast percentage, AML morphological subtype, and relevant prognostic molecular and cytogenetic markers. All patients received standard 7+3 induction chemotherapy and were monitored until recovery of blood counts, Day 42 post-induction, or death—whichever occurred first during the initial cycle of treatment. Remission status was evaluated via bone marrow examination.

Treatment response was categorized according to the European LeukemiaNet (ELN) criteria. Complete remission (CR) was defined by the presence of <5% blasts in the bone marrow, absence of circulating blasts and blasts containing Auer rods, no evidence of extramedullary disease, an absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L, and a platelet count $\geq 100 \times 10^9$/L. CR with incomplete hematologic recovery (CRi) fulfilled all criteria for CR except in cases of persistent neutropenia (ANC $< 1.0 \times 10^9$/L) or thrombocytopenia (platelet count $< 100 \times 10^9$/L). Partial remission (PR) was defined by fulfilment of all hematologic parameters for CR with a bone marrow blast percentage between 5–25%, accompanied by at least a 50% reduction from the pretreatment blast count. Not in remission (NR) Bone marrow blasts >25% and/or presence of circulating blasts and/or presence of extramedullary disease. Induction mortality was when death occurring within 42 days after initiating chemotherapy. Remission included cases of CR and CRi.

Data were analyzed using SPSS version 23.0. Numerical variables—including age, white blood cell (WBC) count, and bone marrow blast percentage—were summarized using mean ± standard deviation (SD) and median values. Categorical variables such as gender, AML subtype, cytogenetic risk classification, remission status, and mortality rates were presented as frequencies and percentages. To account for potential effect modifiers, data

were stratified based on age, WBC count, and blast percentage. Following stratification, the chi-square test was applied to assess associations with remission status, with a p-value ≤ 0.05 considered statistically significant.

RESULTS

A total of 88 patients were enrolled in the study, with a mean age of 29.18±10.6 years.54 (61.4%) patients belonged to the 15-30 years age group, and 34 (38.6%) were in the 31-55 years age group. Gender distribution revealed 50 (56.8%) males and 38 (43.%) females, establishing a male-to-female ratio of 1:1.3. The mean blast cell count in the bone marrow before treatment was 75±21.9%. According to the French-American-British (FAB) classification, the prevalent subtype was AML M2 (50%), followed by AML M4 (15.9%), AML M1 (13.6%), and AML M0, M5, and AML-MRC (6.8% each).

Risk stratification based on European Leukemia Net criteria revealed 45.5% of patients with intermediate risk, 31.8% with favorable risk, and 22.7% with adverse risk disease. The most frequent chromosomal translocation, t(8;21), occurred in 13% of patients, with NPM1 mutation being the most common molecular mutation (22%). FLT3 was detected in 11.4% of patients. Remission was successfully achieved in 71.6% of patients, while 4.5% did not undergo repeat biopsy due to mortality, and 23.9% were refractory to chemotherapy. The study observed a 4.5% frequency of induction mortality.

Statistical analyses demonstrated no significant impact of age groups on the remission rate (p-value 0.116) or blast cell percentage (p-value 0.325). Similarly, the leukocyte count at presentation showed no significant relationship with the frequency of remission (p-value 0.359). Additionally, there was no significant effect of age on the mortality rate (p-value 0.104), blast cell percentage on induction mortality rates (p-value 0.852), or total leukocyte count at presentation on induction mortality rate (p-value 0.562).

TABLE-I

Demographic distribution of the study population

Age	
Mean age	29.18±10.6 years
Age groups	
15-30 years	54 (61.4%)
31-55 years	34 (38.6%)
Gender	
Male	50 (56.8%)
Female	38 (43.2%)
Mean blast cell count	75±21.9%
FAB sub types	
AML M2	50%
AML M4	15.9%
AML M1	13.6%
AML M0	6.8%
AML M5	6.8%
AML-MRC	6.8%
Risk stratification based on ELN	
Favorable	31.8%
Intermediate	45.5%
Adverse risk	22.7%

TABLE-II

Frequency of remission and induction mortality

		Frequency	Percent
Remission post chemo-therapy	Remisson	63	71.6%
	Refractory	21	23.9%
	Not done	4	4.5%
Induction mortality	Alive	84	95.5%
	Death	4	4.5%
	Total	88	100%

TABLE-III

Association between remission and age / blast percentage

Variable	Remis-sion (n, %)	Refrac-tory (n, %)	Not As-sessed (n, %)	Total (n)	P-Value
Age Group					
15–30 years	40 (74.1%)	10 (18.5%)	4 (7.4%)	54	0.116
31–55 years	23 (67.6%)	11 (32.4%)	0 (0.0%)	34	
Blast % in BM					
< 85%	34 (72.3%)	11 (23.4%)	2 (4.3%)	47	0.325
≥ 85%	29 (70.7%)	10 (24.4%)	2 (4.9%)	41	

TABLE-IV

Association between remission status and total leukocyte count

Total Leukocyte Count	Remission (n,%)	Refractory (n,%)	Not Assessed (n,%)	Total (n)	P-Value
< 50,000 /cmm	43 (76.8%)	11 (19.6%)	2 (3.6%)	56	0.359
> 50,000 /cmm	20 (62.5%)	10 (31.2%)	2 (6.2%)	32	

TABLE-V

Association between induction mortality and total leukocyte count

Total Leukocyte Count	Alive (n,%)	Death (n,%)	P-Value
< 50,000 / cmm	54 (96.4%)	2 (3.6%)	0.562
> 50,000 / cmm	30 (93.8%)	2 (6.2%)	

DISCUSSION

An essential step to achieve a cure for AML involves reducing the leukemic burden through intensive cytotoxic chemotherapy to induce complete remission (CR). Upon reaching CR, to sustain remission and achieve long-term cure, patients may undergo additional cycles of cytotoxic chemotherapy or hematopoietic stem cell transplantation.[14] Seminal investigations by the Cancer and Leukemia Group B (CALGB) during the 1980s identified the most efficacious albeit still imperfect induction regimen: three days of daunorubicin (45–60 mg/m^2) combined with a seven-day course of cytarabine (100–200 mg/m^2.[15] Subsequent investigations have focused on enhancing the efficacy of remission induction, with the overarching aim of improving overall survival (OS) as a clinically meaningful outcome. This study was conducted to determine remission rate and induction mortality in patients undergoing the 7+3 chemotherapy regimen within our population.

In our study, 88 patients were enrolled, with a mean age of 29.18±10.6 years. The majority of patients (61.4%) belonged to the younger age group, while 38.6% were in the older age group. Among the participants, 56.8% were male and 43.6% were female. The mean blast percentage in the bone marrow prior to treatment initiation was 75±21.9%. The most prevalent AML subtype in our study was AML M2, accounting for 50% of patients, followed by AML M4 (15.9%), AML M1 (13.6%), and AML M0, M5, and AML-MRC (6.8% each). Remission was achieved in 71.6% of the total patients, while 4.5% of patients did not have their remission assessed due to death during the induction phase. Additionally, 23.9% of patients were refractory to chemotherapy. The observed frequency of mortality during the induction phase in our study cohort was 4.5%, which aligns with reported rates in comparable clinical settings utilizing the standard 7+3 induction protocol.

Our findings align with previous studies and yield even better results, particularly when compared to older studies conducted in our region. Notably, our results remain consistent with more recent studies conducted in Western countries. A multicenter study in India reported a CR rate of 52.8% and an induction mortality rate ranging from 6.1% to 43% across different centers.[16] A single-center study in India demonstrated a CR rate of 70% and an induction mortality rate of 18.4%.[17] While no similar recent studies were found in Pakistan, a single-center study from 1996 reported CR and induction mortality rates of 65% and 29%, respectively.[12] Another study conducted in 2017 found similar treatment outcomes, with an induction mortality rate of 4.8% and increased mortality observed in patients over 55 years. Our study did not include cases over 55 years, but induction mortality in younger patients was comparable to the reported findings. In this same study, the remission rate after chemotherapy was 71%, and remission was more common in younger patients, which is consistent with our study.[18] Another study highlighted the benefits of a 7+3 regimen with daily infusion, including reduced hospital stay and decreased financial burden associated with chemotherapy.[19] A retrospective study reviewing 113 patients treated with the 7+3 regimen reported a remission rate of 87.6%, which is similar to our study.[20] A study conducted at the National Institute of Medical Sciences and Nutrition Salvador Zubirán, Mexico City, between

November 2010 and November 2016, involving 40 patients aged 18–55 years, reported outcomes comparable to those observed in our cohort. The remission rate was 76.2%, the induction mortality rate was 5%, and the mean overall survival was 17.2 months.[21] Additionally, earlier reports from the same institution documented complete remission (CR) rates of 39.5% following a single cycle of the 7+3 regimen, which increased to 62.6% with two cycles in patients with a median age of 44 years (range: 15–79 years).[22]

Regarding the influence of various patient factors on treatment outcomes, older age has historically been considered a poor prognostic marker.[18] Our study demonstrated a trend toward higher remission rates in younger patients; however, this difference did not reach statistical significance. This observation may be influenced by the limited sample size and the disproportionate distribution of patients within the younger age cohorts. Additionally, neither elevated white blood cell (WBC) count at diagnosis nor blast percentage were found to be significant predictors of treatment response or survival, a finding consistent with previously published data.[20] A review of the literature suggests that the remission rate has been increasing with the use of the 7+3 regimen, accompanied by a decrease in induction mortality rates over time.[10,11,12,22] The reduction in induction mortality is likely due to improvements in supportive care in recent years, as observed worldwide.

Our study has few limitations, including its single-center design, with relative a small population, and a predominantly younger patient population up to the age of 55, which may impact the generalizability of the findings. Exclusion criteria, such as patients leaving before completing induction chemotherapy, introduce potential bias. Resource limitations prevented testing for germline mutations and molecular classification. The study period, spanning from August 2018 to May 2021, may not fully capture evolving treatment practices. The focus on fit patients aged 15-55 may restrict the applicability of the results to older or less fit individuals. As this study yields important clinical insights, its limitations should be carefully considered when interpreting the findings.

CONCLUSION

The 7+3 standard chemotherapy regimen is an intensive yet effective induction chemotherapy for fit patients to achieve remission. While historically linked to significant treatment-related mortality, the progress made in supportive care has rendered mortality rates associated with 7+3 chemotherapy acceptable in the present day.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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2	**Mussawair Hussain:** Data analysis, Manuscript writing, Draft making.
3	**Murad Ali:** Draft making.
4	**Qamar Un Nisa Chaudhry:** Methodology, supervision..
5	**Ghassan Shamshad:** Data collection, Supervision.
6	**Fayyaz Hussain:** Data analysis.
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