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Frequency of Induction-Related Mortality in Patients of Acute Myeloid Leukemia - Experience from a Resource Limited Country

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Treatment-related mortality during remission induction (also known as induction-related mortality) is a significant contributing factor to poor outcome of acute myeloid leukemia (AML) patients. This is true especially for resource limited countries where there is dearth of adequate supportive care. This study is carried to analyze the frequency of induction mortality in AML patients in Pakistan and the factors that contribute to it.

Methodology: This descriptive case series was conducted in AML patients admitted in INMOL Hospital, Lahore from November 2017 to April 2018. 80 Patients aged 5-50 years of age with de-novo AML were included in the study. Their progress over 28 days following start of induction chemotherapy, including complications experienced and the outcome at end of 28 days was observed. All patients received prophylactic anti-fungal therapy as part of supportive care.

Results: The progress and outcomes of 80 patients were analyzed including 8 patients less than 15 years of age and 4 patients of acute promyelocytic leukemia. The induction-related mortality was 27.5% (n=22). Of the patients alive at the end of 28 days of start of induction, 38 achieved complete morphological remission (65.5%). Poor performance status was associated with higher induction mortality (*P* = .01). The cause of death in 90% of the patients was sepsis and fulminant infections.

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Conclusion: The frequency of induction mortality in our population was 27.5%. This is a significantly high number when compared with data from the developed resource abundant countries. Thus it highlights the importance of allocation of increased resources to provide adequate supportive measures and infection control for this population.

Keywords: Acute myeloid leukemia; induction-related mortality; performance status; supportive care; resource-limited countries.

ABBREVIATIONS

1. *AML: Acute myeloid leukemia*
2. *APML: Acute promyelocytic leukemia*
3. *ASCO: American Society of Clinical Oncology*
4. *ATRA: All Trans Retinoic Acid*
5. *CN-AML: Cytogenetically Normal Acute Myeloid Leukemia*
6. *CR: Complete Remission*
7. *ECOG: Eastern Cooperative Oncology Group*
8. *HEPA: High-Efficiency Particulate Air*
9. *IDSA: Infectious Diseases Society of America*
10. *INMOL: Institute of Nuclear Medicine and Oncology Lahore*
11. *MD Anderson: Monroe Dunaway Anderson*
12. *MRC: Medical Research Council*
13. *NCCN: National Comprehensive Cancer Network*
14. *SPSS21: Statistical Package for the Social Sciences Version 21*
15. *SWOG: Southwestern Oncology Group*
16. *TLS: Tumor lysis syndrome*
17. *WBC: White blood cell*
18. *WHO: World Health Organization*

1. INTRODUCTION

Acute myeloid leukemia (AML) is a malignant proliferation of poorly differentiated myeloid blast cells in the marrow, peripheral blood and rarely other organs [1]. This results in fever, infections and signs and symptoms of bone marrow failure such as anemia and thrombocytopenia. The diagnosis of AML is established, when >20% of blasts of myeloid lineage are demonstrated in the blood or bone marrow, the lineage being confirmed by Multi-parameter Flowcytometry [2]. It is a genetically and molecularly heterogeneous disease, as reflected in the 11 distinct entities that compose the WHO classification [3].

Throughout the world, the incidence of AML has increased gradually in the past 28 years from 63.84×10^3 in 1990 to 119.57×10^3 cases in 2017 (an increase of 87.3%); with India, China and USA being the countries reporting the highest incidence [4]. The survival data of AML shows better outcome in the developed world (35-40%) as compared to the developing world (20-35%) [5]. This is due to the better health infrastructure, patient support facilities, improved nutrition and infection control in the developed world as compared to resource limited developing countries. Otherwise, the backbone of AML induction treatment (the 7+3 regime) has remained essentially the same globally in the past few decades.

With the 7+3 chemotherapy regimen (Cytarabine and Daunorubicin), the complete remission rate is approximately 60–80% in younger patients and 40–60% in elder patients [6]. However, the challenge in treating AML is not only to attain remission and cure with intense myelosuppressive chemotherapy but also to minimize treatment related mortality by adequate supportive care. Treatment related mortality, is an important cause of therapeutic failure in AML especially during induction, the most intensive treatment phase. It has been seen that the risk of death is maximum in the first four weeks following start of chemotherapy (the induction mortality) and declines rapidly thereafter [7]. This is due to high disease burden, treatment related cytopenias and increase incidence of infections during this phase [8]. In children, even though AML accounts for 15-20% of childhood leukemias, it causes more than half of the disease-related deaths primarily because of treatment related toxicity and mortality [9].

To identify the high risk patients who are particularly prone to death during induction, several scoring systems have been formulated. These have identified factors contributing to increased induction mortality and include age, performance status, complete blood count parameters, metabolic factors and peripheral blood blast percentage [10,11].

There is a significant difference in the induction mortality in the resource abundant and the resource limited countries. Studies conducted in

the United States demonstrate an induction mortality of <5% [7,12]. On the contrary, India has a mortality rate of about 15%-20% [13,14]. In Pakistan the data related to incidence and mortality of this disease is scarce, with one study dating back in 2002 showing induction mortality of 29.1% [15], and one in 2007 showed induction mortality as high as 50% [16]. Another study in pediatric age group in the year 2020 showed a mortality of 19.2% [17].

In this study we aim to identify the frequency of induction mortality in Pakistan in the current decade and the associated factors. A wider spectrum of Pakistani population, with varied socio-cultural, economic and ethnic backgrounds and a wider age group including both adults and children having treatment in a specialized cancer center will be studied. This will help identify the burden of mortality during induction of AML, and to help allocate appropriate health-care resources towards the higher-risk individuals suffering from this disease in our resource limited country.

2. MATERIALS AND METHODS

In this descriptive case series, data was collected in a predesigned proforma of all patients of Acute Myeloid Leukemia enrolled from 1st November 2017 to 30th April 2018 in the Hem-oncology wards of INMOL Hospital Lahore. This data included demographic details of patients, baseline disease characteristics and laboratory parameters, course and complications that occurred during induction, the outcome and remission status at the end of induction. Collected data was entered in SPSS 21 and analyzed for description and results.

Quantitative variables i.e. age and duration of illness were measured as mean, median and standard deviation while qualitative variables i.e. gender, cytogenetic data and induction-related mortality were described as frequency and percentages. Patients were stratified in the favorable, intermediate and adverse risk groups according to cytogenetics status [3], and were also categorized according to age, gender, baseline white blood cell (WBC) count on presentation and ECOG status [18]. Groups were compared by using the chi square test taking *P* value ≤ .05 as significant. The primary outcome measure was the frequency of induction related mortality and its association with age, cytogenetics, performance status, white blood cell count, serum bilirubin and serum creatinine. The secondary outcome measure was the frequency of complete remission and induction failure in patients alive at the end of induction period.

All patients aged 5-50yrs, diagnosed with AML on bone marrow biopsy and flow-cytometry and who gave informed consent to be part of the study were included. Informed consent was obtained from both parents in patients whose age was less than 18 years. The age criteria set was in accordance with the institutional selection criteria for admission and treatment of AML patients. Also, the majority of AML patients in Pakistan fall below the 50yrs age bracket unlike the west. Those with relapsed disease, secondary AML, ECOG status >3 and those who left the hospital against medical advice before the completion of 28 days following start of induction were excluded from the study.

Induction mortality was defined as death within 28 days of start of induction chemotherapy due to complications related to AML [10]. Complete Remission was defined in patients who were alive at the end of 28 days and having < 5% blasts in the bone marrow biopsy on morphology. These patients had no extramedullary disease, had neutrophils ≥ 1,000/μL, platelets ≥ 100,000/μL and were transfusion independent [6].

2.1 Treatment Protocol

Patients were categorized according to age. Patients who were less than 15 years of age received ADE chemotherapy according to the Medical Research Council (MRC)-17 pediatric version (containing Daunorubicin 50 mg/m^2/day on day 1, 3 and 5; Cytarabine 100 mg/m^2/dose twice daily day 1–10 and Etoposide 100 mg/m^2/day on day 1–5). Patients above 15 years of age received the '7+3' Regime for induction chemotherapy. This included Cytarabine in a dose of 200mg/m^2 from day 1-7 and Daunorubicin 60mg/m^2 on Day 1, 3 and 5. Patients diagnosed with Acute Promyelocytic leukemia (APML) were started with capsule ATRA (all trans retinoic acid) before induction chemotherapy and continued throughout induction and consolidation till evidence of hematological and clinical remission were obtained. The patients of APML that were of high risk category received the European APML Regime (ATRA + Daunorubicin + Cytarabine) and those with intermediate to low risk disease received Arsenic Trioxide (ATO) and ATRA.

2.2 Supportive Care

Patients remained admitted in the inpatient facility throughout the induction period where supportive care was given and management of complications were done. Only about one third of the patients could benefit from a single HEPA filter in the facility. Platelets were transfused in case of bleeding or when platelet counts dropped to < 10 x 10^9/L (< 20 x 10^9/L in case of APML or febrile patients). Packed red cell concentrates were transfused in case the hemoglobin dropped below 8 g/dl. All patients received prophylactic antifungal treatment in the form of fluconazole or itraconazole. However colony stimulating factors were strictly avoided. Fever in neutropenic patients was defined as a single oral temperature of ≥ 38.3°C (101°F) or a temperature of ≥ 38.0°C (100.4°F) sustained over a 1-hour period [19]. Institutional guidelines were followed for treatment of febrile neutropenia. These guidelines were generated by taking guidance from IDSA and ASCO guidelines and also considering the availability of hospital resources. First line treatment choice was fourth generation cephalosporin and amikacin or meropenem. If fever continued beyond 48 hours Piperacillin-Tazobactam was given. Anti-fungal treatment in the form of Amphotericin B was added empirically if fever continued beyond 96 hours or in case of strong suspicion of fungal infection. In case of suspected or proven venous line infection vancomycin was added.

3. RESULTS

Among the AML patients admitted in the Hem-oncology wards of INMOL Hospital for treatment, 92 fulfilled the inclusion criteria. Of these patients, 12 did not receive induction chemotherapy, either because of death before induction could be started, or because patients left treatment due to financial constraints. These were excluded from the study. 80 patients were finalized for the study in accordance with the selection criteria.

Among these 80 patients 52 (65%) were male and 28 (35%) females. Their baseline characteristics are described in Table 1. The median age was 32 years. 8 patients were less than 15 years old (10%) and given ADE chemotherapy regime. The patients of AML ≥15 years of age received 7+3 induction therapy. All patients had undergone bone marrow cytogenetics and FLT3 testing by PCR (Table 2). The four (5%) patients diagnosed with APML were all adults (>15 years of age) and their diagnosis was confirmed by cytogenetics and/or molecular genetics. Only one patient of high risk APML had CSF cytology sent, which came out negative. The remaining 3 patients of APL were of intermediate risk category.

Patients were categorized according to performance status, WBC count and Cytogenetics. ECOG categorization of performance status was used. Majority i.e. 50 patients (62.5%) were of ECOG 2; 7 (8.8%) were of ECOG 1 and 23 (28.8%) were of ECOG 3. 56% of the patients had WBC count greater than 10,000/mm^3. Regarding biochemical parameters, the majority had normal liver function tests, renal function tests and serum electrolytes. Only 2 patients had raised serum bilirubin and 15 patients had raised serum creatinine. Among the patients enrolled, 4 presented with tumor lysis syndrome (TLS) and chemotherapy was delayed till resolution of TLS.

Risk stratification was done on the basis of cytogenetics in accordance with NCCN guidelines. Majority patients (52; 65%) had intermediate risk cytogenetics while only 16.2% (13 patients) had favorable cytogenetics. 6% of the population was FLT3 positive (extremely poor prognosis). The cytogenetic and molecular abnormalities identified are mentioned in detail in Table 2.

Regarding primary outcome measure, 22 patients died within 28 days of start of induction chemotherapy (induction mortality: 27.5%) (Table 3). Of the patients that were alive, 38 achieved complete remission (CR) confirmed by bone marrow biopsy (CR: 65.5% of alive patients). The remaining were in induction failure. All 4 patients of APML were alive at the end of induction and in CR. The cause of death in 20 out of 22 patients was fulminant infections leading to sepsis (Table 3). Only 2 patients died of uncontrolled hemorrhage. Of the patients dying of sepsis, 75% (n=15) had developed pneumonia and related pulmonary complications before death; 3 had neutropenic enterocolitis and in 2 patients no source of infection could be identified.

71% of patients had ECOG ≤ 2, while 29% of patients had ECOG 3. ECOG 3 was associated with higher induction mortality (P = .01) when compared with patients having ECOG ≤ 2. Thus performance status was the most significant factor influencing induction mortality (Fig. 1). Age was not associated with higher induction

mortality (*P* = .23). Similarly WBC count, cytogenetics and biochemical parameters (creatinine and bilirubin) had no significant association with induction mortality (*P* >.05 for all these parameters) (data not shown). More over cytogenetics did not influence the probability of achieving remission in the patients alive at the end of induction period (*P* = .80) (Fig. 2).

Table 1. Baseline characteristics of acute myeloid leukemia patients

Baseline Characteristics		n (%)	
Age	≤ 15 years	8	(10%)
	> 15 years	72	(90%)
Gender	Male	52	(65%)
	Female	28	(35%)
AML vs APML	AML	76	(95%)
	APML	4	(4%)
White blood cell count (WBC) at presentation (cells/mm^3)	> 10,000	45	(56%)
	4000-10,000	20	(25%)
	< 4000	15	(19%)
Creatinine (µmol/L)	Normal	65	(81.3%)
	Raised	15	(18.7%)
Bilirubin (µmol/L)	Normal	78	(97.5%)
	Raised	2	(2.5%)
ECOG Status	1	7	(8.8%)
	2	50	(62.5%)
	3	23	(28.8%)
Cytogenetics	Favorable	13	(16.2%)
	Intermediate	52	(65.0%)
	Adverse	15	(18.8%)
Treatment Protocol Given (Regime)	MRC-17	8	(10%)
	7+3	68	(85%)
	European APML	1	(1%)
	ATO + ATRA	3	(4%)

Table 2. Cytogenetic/ molecular abnormalities detected in study population

Cytogenetic/Molecular Abnormality	n (%)	
CN-AML[a] (Intermediate Risk)	49	(61.3%)
CN-AML[a] with FLT3 Positivity (Adverse)	5	(6.0%)
t(15;17) (APML) (Favorable)	4	(5.0%)
t(8;21) (Favorable)	6	(7.5%)
Trisomy 8 (Adverse)	5	(6.0%)
Monosomy 7 (Adverse)	3	(3.8%)
Inversion 16 (Favorable)	3	(3.8%)
Complex cytogenetics (Adverse)	2	(2.5%)
Others[b]	3	(3.8%)

Notes: [a] CN-AML: Cytogenetically Normal Acute Myeloid Leukemia
[b] Other cytogenetic abnormalities include: del (5), trisomy 11, t (5;6)

Table 3. Outcome at the End of Induction Period: Induction-related mortality and Frequency of Complete Remission

Outcome		n	TOTAL: n (%)	
Alive	Complete Remission	38	58	(72.50%)
	Induction Failure	20		
Dead	Sepsis/ Infections	20	22	(27.50%)
	Hemorrhage	2		

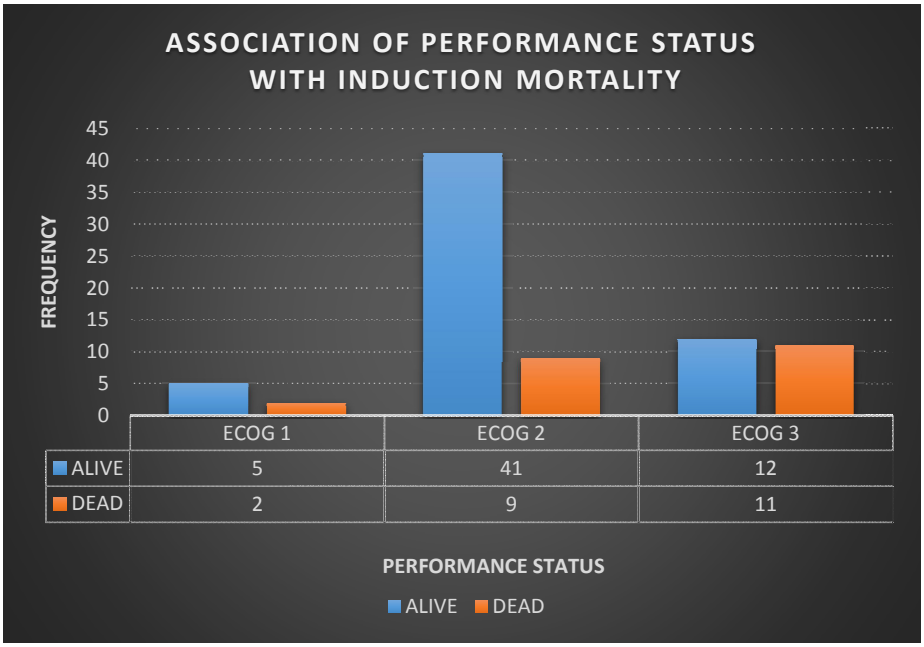

Fig. 1. Association Of Performance Status With Induction Mortality. Poor performance status (ECOG 3) was associated with higher induction mortality (*P* =.01)

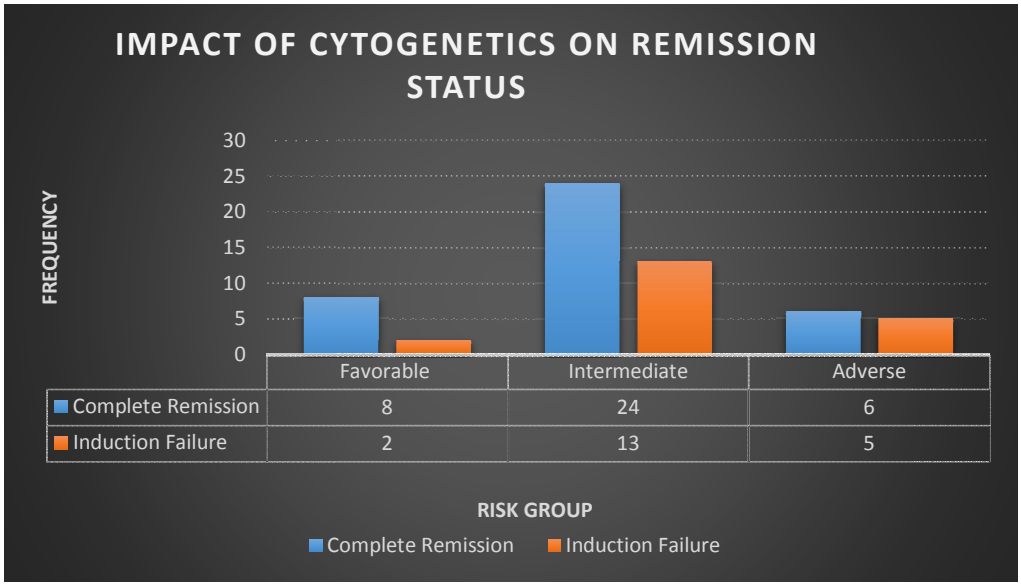

Fig. 2. Impact of Cytogenetics on Remission Status. Cytogenetics had no statistically significant association with frequency of complete remission (*P* = 0.80)

4. DISCUSSION

This study describes the frequency of induction mortality in AML in a specialized cancer center in Pakistan, where standard of care treatment is being offered in a subsidized manner. Acute myeloid leukemia is especially notorious for its dismal outcome, high induction mortality and high relapse rate. The primary goal of this small cases series was to underline the challenges faced in the treatment of acute leukemia mainly during the induction course and recognize induction outcomes for all recorded cases. In Pakistan no formal cancer registry exists to

record its mortality, morbidity and outcomes. Very few studies have been conducted to determine the induction mortality in AML in our population, and to the best of our knowledge this is the only study till date which covers a subset of both the pediatric and adult population.

A 2002 study by Kakepoto et al. demonstrated induction mortality of 29.1% in 55 patients who received treatment in a private hospital [15]. In the patients alive at the end of induction period 65.4% achieved CR. This is comparable to the results of our study where induction mortality is 27.5% and CR rate is 65.5%. However, it also reflects that there has been hardly any improvement in the outcomes of AML patients in our country in almost 16 years. A similar study which aimed to assess the outcomes of AML in Pakistan reported induction mortality as high as 50% [16]. Unlike Pakistan, the west has shown significant improvement in rates of induction mortality, as is evident from data from MD Anderson and SWOG [20]. In these centers the induction mortality declined from 16-18% in the 1990s to 3-4% in the late 2000s.

Induction mortality is a significant challenge in low and middle income countries (LMICs). This is because of delayed presentation, higher disease burden, baseline infections, higher rates of resistant infections and social and financial constraints. It is evident from data that when treating patients of AML, around 85% of cost is spent on providing adequate supportive care to the patients [21]. Many patients simply refuse treatment due to financial constraints, lack of social support and logistic issues. The outcomes of Pakistan are comparable with that of India (mortality ranging from 15-25%) [5, 13, 14] and other resource limited countries [22]. The majority of the deaths (90%) in our study were due to infectious complications and sepsis. The same is true for other resource limited countries where MDR gram negative sepsis and invasive fungal infections are a significant cause of mortality and morbidity [23, 24]. All our patients received antifungal prophylaxis in the form of itraconazole or fluconazole as per resource availability. Voriconazole despite having a better anti-fungal spectrum was not available for primary prophylaxis [25]. Also majority patients couldn't avail the facility of HEPA filter which has a possible role in decreasing frequency of fungal infections [26]. It has also been observed that the presence of baseline infections significantly increase mortality during induction as compared to in those patients where no baseline infections were detected [27]. However, this aspect was not studied in our population.

In the patients aged less than 15 years, 50% (n=4) died during the first four weeks of the start of treatment. Even considering this very small cohort our results are comparable with other LMICs [28]. It has been seen that late presentation, malnutrition and high treatment related mortality result in reduced survival rates of childhood AML in Pakistan [29]. In contrast, the resource-rich countries have a mortality of around 2-5% in the recent years [30]. The poor risk old aged population (>50 years) were altogether excluded from our study.

Regarding the various prognostic factors effecting mortality, only performance status had a statistically significant impact on induction mortality. Other characteristics were also studied including age, WBC count, creatinine and bilirubin, but none had any statistically significant association with mortality. International data also reveals that the most important factor influencing induction mortality is performance status, even more so then age [10]. A wider cohort and prospective trials might help in validating the various treatment-related mortality scores in our population.

The major limitation of our study was that the organisms involved were not studied, and cultures and antibiotic sensitivities were not analyzed. This was primarily because culture sensitivity testing had to be outsourced and majority of the patients couldn't afford its cost. Newer antifungals and antivirals are not easily available as these drugs are not registered in our country and those that are available are not affordable for everyone [31]. Therefore, it would had been appropriate to identify the culprit organisms and their antibiotic sensitivity patterns so that resources could be targeted towards obtaining those specific antibiotics and antifungals. This is an important aspect of supportive care considering that 90% of our patients died due to infection-related complications. Moreover, the cohort of APML patients was very small to adequately represent the mortality risks in these patients. However, the study did highlight how far behind we are in providing adequate supportive measures for our population at risk despite providing standard of care chemotherapeutic agents.

5. CONCLUSION

We conclude that infection is the leading cause of death in the first 28 days following start of AML treatment. Poor performance status significantly enhances risk of acquiring fatal infections and contribute to increased induction mortality. The identification of culprit organisms and targeted therapy against them along with better infection control and supportive measures is paramount in reducing mortality and improving outcome of AML patients.

DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

DECLARATION

- All authors named in the manuscript have contributed significantly in conducting this research.
- The manuscript has been read and approved for submission by all authors.
- This manuscript is original, has not been published before and is not currently being considered for publication elsewhere.
- No conflicts of interests are associated with this publication, and no financial grants were taken for this work that could have influenced its outcome.
- The data that support the findings of this study are available on request from the corresponding author (RT). The data are not publicly available due to hospital's privacy and ethical restrictions.

CONSENT

As per international standard or university standard, respondents' & parental written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The study was approved by the Institutional Ethical Committee of INMOL Hospital, Lahore.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. De Kouchkovsky I, Abdul-Hay M. 'Acute myeloid leukemia: a comprehensive review and 2016 update'. Blood Cancer J. 2016;6(7):e441. DOI:10.1038/bcj.2016.50.
2. Dohner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 2010; 115(3):453–474. DOI:10.1182/blood-2009-07-235358.
3. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20): 2391-2405. DOI:10.1182/blood-2016-03-643544.
4. Yi M, Li A, Zhou L, Chu Q, Song Y, Wu K. The global burden and attributable risk factor analysis of acute myeloid leukemia in 195 countries and territories from 1990 to 2017: estimates based on the global burden of disease study 2017. J Hematol Oncol. 2020;13(1):72. DOI:10.1186/s13045-020-00908-z.
5. Kayal S, Dubashi B, L Cyriac S, Basu D, Kar R, Jacob S et al. Outcome of induction therapy for newly diagnosed acute leukemia in a calendar year: real world data from a tertiary care cancer centre in South India. Archives of Oncology and Cancer Therapy. 2018;1(1):37-47.
6. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129:424–447.

Available:https://doi.org/10.1182/blood-2016-08-733196

7. Buckley SA, Othus M, Estey E, Walter RB. The treatment-related mortality score is associated with non-fatal adverse events following intensive AML induction chemotherapy. Blood Cancer J. 2015;5(1):e276. DOI:10.1038/bcj.2014.97.
8. Goparaju K, O'Brien T. Treatment related mortality (TRM) for AML patients managed at a non-transplant, safety net hospital. J Clin Oncol. 2017;35(15_suppl):e18092. DOI:10.1200/JCO.2017.35.15_suppl.e18092.
9. Zwaan CM, Kolb EA, Reinhardt D, Abrahamsson J, Adachi S, Aplenc R et al. Collaborative efforts driving progress in pediatric acute myeloid leukemia. J Clin Oncol. 2015;33(27):2949-2962. DOI: 10.1200/JCO.2015.62.8289.
10. Walter RB, Othus M, Borthakur G, Ravandi F, Cortes JE, Pierce SA et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. J Clin Oncol. 2011;29(33):4417-4423. DOI:10.1200/JCO.2011.35.7525.
11. Kayal S, Sengar M, Jain H, Bonda A, George B, Kulkarni U et al. Induction related mortality in acute myeloid leukemia: Multivariate model of predictive score from the Indian Acute Leukemia Research Database (INwARD) of the Hematology Cancer Consortium (HCC). Blood. 2019;134(Supplement_1):2615. Available:https://doi.org/10.1182/blood-2019-127623.
12. Handa S, Gupta K, Sidhu J, Petrone G, Rajeeve S, Jatwani K. Etiologies and predictors of 30-day readmission in patients undergoing induction chemotherapy for acute myeloid leukemia. Blood. 2019; 134(Supplement_1):4759. Available:https://doi.org/10.1182/blood-2019-132180.
13. Kumar H, Mehra N, Ganesan P, Radhakrishnan V, Dhanushkodi M, P K J et al. Patterns of infection and mortality associated with intensive AML induction therapy: 10 Year experience from a tertiary cancer centre in India. Blood. 2018;132(Supplement 1):4008. Available:https://doi.org/10.1182/blood-2018-99-119919
14. Bahl A, Sharma A, Raina V, Kumar L, Bakhshi S, Gupta R, Kumar R. Long-term outcomes for patients with acute myeloid leukemia: a single-center experience from AIIMS, India. *Asia Pac* J Clin Oncol. 2015;11(3):242-252. DOI:10.1111/ajco.12333.
15. Kakepoto G N, Burney I A, Zaki S, Adil S N. Khurshid M. Long-term outcomes of acute myeloid leukemia in adults in Pakistan; J Pak Med Assoc. 2012;52(10):482-486.
16. Ullah K, Ahmad P, Raza S, Satti T, Chaudhry Q, Akhtar F et al. Management of acute myeloid leukemia - 5 years' experience at Armed Forces Bone Marrow Transplant Centre, Rawalpindi. J Pak Med Assoc. 2007;57(9):434-439.
17. Ghafoor T, Khalil S, Farah T, Ahmed S, Sharif I. Prognostic factors in childhood acute myeloid leukemia; Experience from a developing country. Cancer Rep (Hoboken). 2020;3(5):e1259. DOI:10.1002/cnr2.1259.
18. Comis R. ECOG Performance Status - ECOG-ACRIN [Internet]. ECOG-ACRIN. 2021. Available from: https://ecog-acrin.org/resources/ecog-performance-status [Accessed 22nd March 2021].
19. Taplitz R, Kennedy E, Bow E, Crews J, Gleason C, Hawley D et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. J Clin Oncol. 2018;36(30):3043-3054. DOI:10.1200/JCO.18.00374.
20. Othus M, Kantarjian H, Petersdorf S, Ravandi F, Godwin J, Cortes J et al. Declining rates of treatment-related mortality in patients with newly diagnosed AML given 'intense' induction regimens: a report from SWOG and MD Anderson. Leukemia. 2013;28(2):289-292. DOI:10.1038/leu.2013.176.
21. Arya D, Parikh B, Shah P, Patel K, Shukla S, Anand A et al. Cost of treatment of acute myeloid leukemia – experiences from a developing country. Ann Oncol. 2012;23(Supplement 9):ix356. Available:https://doi.org/10.1016/S0923-7534(20)33649-8.
22. Campos C, Caldas L, Silva L, Botura M, Almeida A, Schriefer A et al. 10-year real-world data on acute myeloid leukemia: The paradigm of a public health center in Brazil. Blood. 2020;136(Supplement 1): 33-34.

Available:https://doi.org/10.1182/blood-2020-140858.

23. Nganthavee V, Phutthasakda W, Atipas K, Tanpong S, Pungprasert T, Dhirachaikulpanich D et al. High incidence of invasive fungal infection during acute myeloid leukemia treatment in a resource-limited country: clinical risk factors and treatment outcomes. Support Care Cancer. 2019;27(9):3613-3622.
DOI:10.1007/s00520-019-04720-5.
24. Lien M, Chou C, Lin C, Bai L, Chiu C, Yeh S et al. Epidemiology and risk factors for invasive fungal infections during induction chemotherapy for newly diagnosed acute myeloid leukemia: A retrospective cohort study. PLoS One. 2018;13(6): e0197851.
DOI:10.1371/journal.pone.0197851
25. Zabalza A, Gorosquieta A, Equiza EP, Olavarria E. Voriconazole and its clinical potential in the prophylaxis of systemic fungal infection in patients with hematologic malignancies: a perspective review. Ther Adv Hematol. 2013;4(3): 217-30.
DOI: 10.1177/2040620713481796.
26. Leventakos K, Lewis R, Kontoyiannis D. Fungal infections in leukemia patients: How do we prevent and treat them? Clin Infect Dis. 2010;50(3):405-415.
Available:https://doi.org/10.1086/649879.
27. Pandian J, Raghavan V, Manuprasad A, Shenoy P, Nair C. Infection at diagnosis—a unique challenge in acute myeloid leukemia treatment in developing world. Support Care Cancer. 2020;28(11):5449-5454.
DOI:10.1007/s00520-020-05379-z.
28. Philip C, George B, Ganapule A, Korula A, Jain P, Alex AA et al. Acute myeloid leukemia: challenges and real world data from India. Br J Haematol. 2015;170(1): 110-7.
DOI:10.1111/bjh.13406.
29. Fadoo Z, Mushtaq N, Alvi S, Ali M. Acute myeloid leukemia in children: experience at a tertiary care facility of Pakistan. J Pak Med Assoc. 2012;62(2):125-8.
30. Gamis A, Alonzo T, Meshinchi S, Sung L, Gerbing R, Raimondi S et al. Gemtuzumab Ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Children's Oncology Group trial AAML0531. J Clin Oncol. 2014;32(27): 3021-3032.
DOI:10.1200/JCO.2014.55.3628.
31. Ullah K, Ahmed P, Raza S, Mahmood T, Khan B. Comparison of different chemotherapy regimens in the management of acute myeloid leukemia - 5 years' experience from Pakistan. Blood. 2007;110(11):4349.
Available:https://doi.org/10.1182/blood.V110.11.4349.4349.

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