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ORIGINAL ARTICLE

Treatment patterns and comparative analysis of non-intensive regimens in elderly acute myeloid leukemia patients—a real-world experience from India

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Abstract

Elderly patients with acute myeloid leukemia have a poor prognosis. Data from developing countries is sparse in the literature. In this retrospective study, 402 patients aged ≥ 60 years, diagnosed between Jan 2013 and Dec 2017, were analyzed for treatment patterns and survival. Median age of the whole cohort was 68 years (range 61–84). A total of 213 patients (53.3%) refused care; 188 patients (46.7%) received either BSC, LDAC, or HMA. Survival (in months) was 3.9, 6.4, and 1.2 with LDAC, HMA, and BSC, respectively. One-year survival was 17.2% and 6% with HMA and LDAC, respectively ($P = 0.02$). Overall response rate (ORR) did not differ between HMA and LDAC group ($p = 0.12$). HMA cohort had higher complete responses (20.6% vs 7.4%, $p = 0.02$), stable disease (32.7% vs 13.5%, $p = 0.02$), and transfusion independence (TI) (46.5% vs 22.2%, $p = 0.01$). Survival did not differ between the groups if the patients achieved ORR (12.3 vs 9.8 $p = 0.2$) or TI (11.6 vs 6.4 $p = 0.2$). Stable disease with HMA led to longer survival (8.1 vs 5.3 $p = 0.01$). HMAs were more effective than LDAC irrespective of cytogenetic risk category and blasts, of note HMAs improved survival of poor risk patients (5.6 vs 2.9 $p = 0.004$). HMA treatment (HR = 0.48; 95% 0.29–0.79, $p = 0.004$) and transfusion independence (HR = 0.2; 95% 0.1–0.3, $p = 0.0001$) predicted survival in multivariate analysis. Neutropenia and febrile neutropenia were frequent in HMA. Thrombocytopenia was the common adverse event with LDAC. Novel and cost-effective drugs are essential to improve the prognosis of these patients.

Keywords LDAC-low dose cytarabine · HMA-hypomethylating agents · AML-acute myeloid leukemia · TI-transfusion independence

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Introduction

Acute myeloid leukemia is the most common acute leukemia in adults. Median age at diagnosis is 67 years [1]. AML being the disease of elderly, burden of AML is expected to increase as the world population ages [2]. The prognosis of these patients is dismal, 5-year survival rate being less than 5% compared to 40% in the younger population [3]. Disease in elderly has adverse biology and elderly patients have higher comorbidities which preclude them for curative intensive chemotherapy [4]. Hence, these patients have limited therapeutic options. Low-dose cytarabine (LDAC) was effective in a multi-institution study, where LDAC 20 mg twice daily for 10 days resulted in higher CR rate compared to hydroxyurea (18 versus 1%) [5]. Since AML in the elderly is associated with the epigenetic changes, secondary to the mutations in the DNA methylating pathway [6], epigenetic modifiers like hypomethylating agents are effective in these patients. Azacytidine and decitabine have shown clinical benefit both in the RCTs [7, 8] and in the retrospective studies, albeit the survival was lower than in observational studies [9–12]. Currently, hypomethylating agents and low-dose cytarabine form the mainstay of the treatment in patients not eligible for intensive chemotherapy.

Much of the data concerning the treatment and survival of elderly AML patients are from the developed world. Studies from the developing nations like India are scarce in the literature. Developing nations face challenges which are unique to them, like an inadequate follow-up, lack of supportive care, inaccessible health care [13], and modified protocols for treatment [14–16]. Hence, we envisaged a study which would give an account of the treatment patterns and the prognosis of these patients. To our knowledge, this is the first comprehensive analysis from India with respect to the management of elderly AML patients.

Study design and patient eligibility

Retrospective analysis of all the newly diagnosed, immunophenotypically confirmed de novo or secondary AML (> 20% blasts) aged more than 60 years at our institute between January 2013–December 2017 was performed. Demographic data, investigation reports, and treatment details were collated from the hospital information system. The study was approved by the local ethics committee. Consent was obtained from all the patients before the treatment. Patients were assigned different risk groups according to MRC criteria [17]. The patients who received BSC with or without hydroxyurea or non-intensive chemotherapy (LDAC or HMA) were analyzed.

Treatment

Patients who opted for HMA received either azacytidine (AZA) 100 mg/m^2/day for 7 days every 28 days or decitabine (DEC) 20/mg/m^2 for 5 days every 28 days. Low-dose cytarabine (LDAC) was administered at 20 mg/day BD every 28 days. Best supportive care with or without hydroxyurea included transfusion of blood products, treatment of infections as per the hospital policy. Patients received antimicrobial prophylaxis, blood product transfusion support, according to established local practice. Leukemia-specific treatment (HMA/LDAC) was continued until relapse, progressive disease, death, unacceptable toxicity, lack of clinical benefit, inter-current illness preventing treatment, or at patient request.

Objectives and end points

The primary objective was to determine and compare the overall survival (OS), in patients who received leukemia-specific treatment or best supportive care. Secondary objective was to compare response rates and survival across different groups and adverse events in patients who received LDAC and HMA. Event for OS was death due to any cause. Patients were censored at the date of the last contact or lost to follow-up.

Response and adverse event assessment

Bone marrow was assessed for remission status after four cycles of treatment and response classified according to the International Working Group criteria for AML. Stable disease was defined as not meeting criteria for any other treatment response (i.e., CR, CRi, PR, disease progression, or early death.) Transfusion independence (TI) was defined as no requirement of RBC/platelet transfusion for eight consecutive weeks during the course of therapy [18]. Death within 8 weeks was defined as early death [19]. Details of adverse events were collected by reviewing patient charts and were graded according to the national cancer Institute common toxicity criteria for adverse events (version 4.0).

Statistical analysis

Statistical analysis was performed using SPSS version 22. Descriptive statistics were used to describe patients and disease characteristics. Demographic, biological, and clinical characteristics were compared using Chi-square test/Fisher's exact/Kruskal-Wallis test for categorical variables and ANOVA/Mann-Whitney *U* test for continuous variables. Chi-square/Fisher's exact test and *t* tests were used to compare response rates, transfusion independence, adverse events between LDAC and HMA groups. Estimated probabilities of

overall survival were calculated using the Kaplan-Meier method, and the log-rank test was used to evaluate differences between survival distributions. Hazard ratio (HR) and 95% confidence interval were calculated using Cox proportional hazards model stratified by age, performance status, cytogenetic risk, bone marrow blasts, response, and transfusion independence. Multivariate analysis for the survival was done using Cox regression method. Significance was set at $p < 0.05$.

Results

Patient characteristics

A total of 402 patients were diagnosed with non-M3 AML who were > 60 years from Jan 2014 to December 2017. Of these, 213 patients (53.3%) refused care due to various factors like lack of family support, unable to relocate, and financial constraints. A total of 139 (34.5%) patients received chemotherapy [81 patients (58.3%) received low-dose cytarabine and 58 patients (41.7%) received hypomethylating agents], 49 patients (12.2%) received best supportive care. A total of 188 patients (46.7%) who received either best supportive care (BSC), low-dose cytarabine (LDAC), or hypomethylating agents (HMA) were included in the final analysis.

Demographic and disease characteristics of the patients in different groups are summarized in Table 1. Median age was 68 years (range 61–84) for the whole cohort. Median age was higher in BSC cohort 71 years (range 61–84) than LDAC cohort ($p = 0.001$) and HMA cohort ($p = 0.001$). Patients in the HMA were younger compared to LDAC (64 vs 68 years, $p = 0.001$). Majority of secondary AML (51.4%) received either best supportive care or LDAC (40%). Patient in the HMA group had better performance status when compared to LDAC ($p = 0.04$) and BSC group ($p = 0.0001$). Patients in the HMA group had higher hemoglobin at presentation than patients in LDAC ($p = 0.03$) and BSC group ($p = 0.04$). Six patients in HMA group and eight patients in LDAC group were RBC transfusion independent at presentation. Total leucocyte count ($p = 0.3$), bone marrow blasts ($p = 0.2$), and platelet count ($p = 0.8$) did not vary between the cohorts. Groups did not differ with respect to cytogenetic risk category (i = 0.8).

Response to treatment and survival

Median four cycles (range 1–20) of HMA and two cycles (1–18) of LDAC were received by the patients. Response to the treatment in LDAC and HMA group is shown in Table 2. Overall response rate (ORR) did not differ between HMA and LDAC group ($p = 0.12$); nonetheless, HMA cohort had higher complete responses (20.6% vs 7.4%, $p = 0.02$) and stable disease (32.7% vs 13.5%, $p = 0.02$). Forty-one patients (48.1%) in LDAC group and 11 patients (17.3%) in HMA group ($p = 0.0001$) progressed before or at the first assessment for response. In patients who were RBC transfusion dependent, 24 patients (46.1%) in HMA group and 18 patients (24.6%) in LDAC group ($p = 0.02$) attained TI. Sixty-three percent (12/19) of patients with stable disease attained TI in HMA group compared to 36% (4/11) patients in LDAC group ($p = 0.02$). Hemoglobin at presentation was predictive of response and attainment of transfusion independence; adjusted odds ratio after controlling for age, performance status, treatment, risk category, and blasts was 2.8 (95% CI 1.6–4.8, $p = 0.001$) for ORR and 0.3 (95% CI 0.16–0.54, $p = 0.001$) for TI.

Median survival was 1.2 months (95% CI 1.1–1.2) for BSC, 6.4 months (95% CI 4.2–8.5) for HMA, and 3.9 months (95% 2.5–5.2) for LDAC. Both LDAC and HMA provided a significant survival advantage over BSC. The hazard ratio for LDAC was 0.31 (95% CI 0.21–0.46) and HMA was 0.14 (95% C I 0.09–0.22) (Fig. 1). One-year survival rate was 17.2% with HMA compared to 6% with LDAC ($p = 0.03$). HMA treatment reduced the hazard by 66% compared to LDAC (HR = 0.44 95% C I 0.30–0.64, $p = 0.00007$).

In patients who received either low-dose cytarabine or hypomethylating agents, survival was compared across the different subgroups of AML. Patients with response to the treatment (ORR) showed no difference in survival 12.3 months vs 9.8 months (HR = 0.59, 95% CI 0.2–1.3, $p = 0.21$); nevertheless, patients achieving stable disease with HMA, lived longer (8.1 months vs 5.3 months, HR = 0.25, 95% 0.1–0.6, $p = 0.01$). Though not statistically significant, transfusion independence (TI) resulted in longer survival with HMA (11.6 months vs 6.4 months, $p = 0.2$, HR = 0.62, 95% CI 0.3–1.2). HMAs benefitted the patients less than 70 years (HR = 0.54 95% 0.3–0.7, $p = 0.002$); however, the same was not true in patients over the age of seventy 0.47 (HR = 0.1–1.3, $p = 0.16$). Interestingly, in patients with ECOG-2 performance status, HMA treatment resulted in longer survival (5.6 vs 3.6 months $P = 0.004$, HR 0.29, 95% CI 0.1–0.6). HMAs were effective compared to LDAC irrespective of the blast count and across the cytogenetic risk category (Table 3).

In the multivariate analysis, treatment with hypomethylating agents (HR 0.48, 95% CI 0.29–0.79, $p = 0.004$) and transfusion independence (HR 0.2, 95% CI 0.1–0.3, $p = 0.0001$) were predictive of survival; it was adjusted for ECOG 1 and 2, LDH, blast percentage, risk category, and age (Table 4).

Toxicity assessment

Neutropenia (68.9%) and thrombocytopenia (76.5%) were the most frequent complication in the HMA cohort and LDAC cohort, respectively. Patients experienced 32 episodes of febrile neutropenia in the HMA group and 21 episodes in the LDAC group ($p = 0.01$) (Table 5). Eight-week mortality was

Table 1 Patient characteristics in different groups

	BSC ($N = 49$)	LDAC (N-81)	HMA ($N = 58$)	P value
Age	71 (61–84)	68 (62–74)	64 (61–74)	0.0001
60–70	19 (38.7%)	44 (55.4%)	51 (88%)	0.003
> 70	30 (61.2%)	37 (44.6%)	7 (11.9%)	0.02
Sex				
F	24 (48.9%)	26 (32.1%)	19 (32.8%)	
M	25 (51.0%)	55 (67.9%)	39 (67.2%)	0.3
AML				
Den ovo	31 (63.2%)	67 (82.8%)	55 (94.9%)	
Secondary	18 (36.8%)	14 (17.2%)	3 (5.1%)	0.0001
Performance status				
1	10 (20.4%)-	29 (35.8%)	43 (74.2%)	
2	22 (44.9%)	23 (28.4%)	15 (25.8%)	0.0001
3	17 (34.7%)	29 (35.8%)	–	
TLC mean ± 2SD	32,225 ± 5496	32,691 ± 3757	23,265 ± 4459	0.3
Blasts				
20–30%	23 (46.9%)	26 (32.1%)	27 (46.5%)	
> 30%	26 (53.1%)	55 (67.9%)	31 (53.5%)	0.2
LDH	650 ± 229	584 ± 212	580 ± 156	0.5
Mean ± 2SD Cytogenetics				
favorable	11 (22.4%)	24 (29.6%)	14 (24.2%)	
Intermediate	21 (42.8%)	29 (35.8%)	22 (37.9%)	
Unfavorable	17 (34.6%)	28 (34.6%)	22 (37.9)	0.8
Hemoglobin Mean ± 2SD	6.5 ± 1.4	6.6 ± 1.0	6.7 ± 1.1	0.04
Platelets Mean ± 2SD	23,450 ± 24,576	28,580 ± 24,191	29,890 ± 25,560	0.8

AML acute myeloid leukemia, *LDH* lactate dehydrogenase, *TLC* total leucocyte count

19% and 17.2% in HMA and LDAC cohorts, respectively (Table 2).

Eight patients succumbed to treatment-related complications and three patients due to non-responsive disease. In HMA cohort, the non-responsive disease was the frequent cause of the early death in LDAC group.

Rates of hospital admission per patient-year of follow-up were 1.52 for HMA and 1.47 for LDAC cohort (RR 0.93, 95% CI 0.7–1.4, $p = 0.9$). Time spent in hospital per patient-year of follow-up for management of complications was 15.3 days in HMA cohort and 14.1 days in LDAC cohort (RR 0.92, 95% 0.7–1.2, $p = 0.8$).

Discussion

Prognosis of the patients with elderly AML is poor across the world, more so in the countries with limited resources [13]. To our knowledge, ours is the first study from India giving an account of the treatment patterns and prognosis of these patients. An overwhelming majority of our patients (53%) either declined care or received low-dose cytarabine (20.1%) as opposed to intensive chemotherapy for eligible patients or hypomethylating agents for non-fit patients in developed countries [20, 21, 22, 23]. This is

Table 2 Comparison of response between two groups

	HMA N = 58	LDAC $N = 81$	P value
Median cycles (range)	4 (1–20)	2 (1–18)	0.18
CR	12 (20.6%)	6 (7.4%)	0.02
PR	6 (10.4%)	11 (13.5%)	0.02
ORR	18 (31%)	17 (20.9%)	0.12
SD	19 (32.7%)	11 (13.5%)	0.02
Progression	10 (17.3%)	39 (48.1%)	0.0001
Transfusion independence (TI)	27 (46.5%)	18 (22.2%)	0.01
Early death	11 (19%)	14 (17.2%)	0.48

CR complete response, with incomplete count recovery, *PR* partial response, *ORR* overall response rates, *SD* stable disease

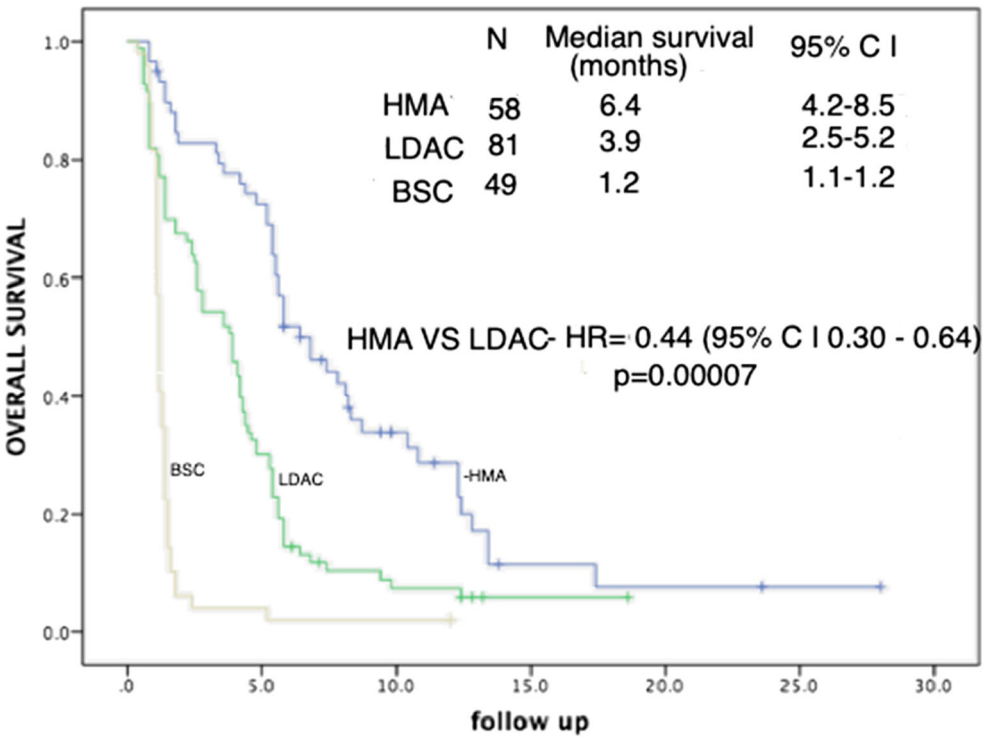

Fig. 1 K M Survival curves of patients with Best supportive care(BSC), Low dose cytarabine (LDAC) and Hypomethylating agents(HMA)

due to the high cost of HMA 24,000 ($360) compared to LDAC 1600 ($24) and high treatment-related mortality [12, 13]. A total of 52% and 35% of the ECOG-1 patients received HMA's and LDAC, respectively. Merely 8% of the secondary AML received hypomethylating agents. This indicates physicians preferred HMA in good performance status and de novo AML patients to maximize the clinical benefit which is consistent with the previous studies that performance status and the disease biology are predictive of good prognosis [24].

Table 3 Comparison of survival in various subgroups

	HMA	LDAC	Hazard ratio (95% CI)	Long rank *p*
Response				
ORR	12.3 (10.3–14.2)	9.8 (4.9–14.6)	0.59 (0.2–1.3)	0.2
SD	8.1 (4.2–11.9)	5.3 (4.6–5.9)	0.25 (0.1–0.6)	0.01
Progression	5.6 (4.6–5.8)	2.3 (1.5–3.2)	0.16 (0.1–0.3)	0.002
Age				
60–70	6.4 (4.3–8.4)	5.2 (1.2–8.1)	0.54 (0.3–0.7)	0.002
> 70	3.9 (2.3–5.4)	2.8 (1.1–4.4)	0.47 (0.1–1.3)	0.16
ECOG				
1	7.6 (5.2–9.4)	5.6 (5.2–5.9)	0.7 (0.4–1.4)	0.6
2	5.6 (4.0–7.1)	3.6 (1.7–5.4)	0.29 (0.1–0.6)	0.004
Blasts (%)				
20–30	8.3 (4.6–11.9)	4.3 (2.8–5.7)	0.48 (0.2–0.9)	0.01
> 30	5.7 (4.8–6.1)	2.8 (1.1–4.0)	0.46 (0.3–0.9)	0.02
Cytogenetic risk				
Good	8.6 (5.9–10.8)	4.1 (3.7–4.6)	0.40 (0.1–1.7)	0.01
Intermediate	6.9 (3.1–7.2)	3.8 (1.7–5.8)	0.37 (0.1–0.7)	0.003
poor	5.6 (5.05–6.14)	2.9 (2.1–3.4)	0.43 (0.2–0.8)	0.004
Transfusion independence (TI)				
Yes	11.6 (9.9–13.2)	6.4 (3.4–6.1)	0.62 (0.3–1.2)	0.2
No	4.9 (1.1–8.9)	2.7 (2.2–4.1)	0.47 (0.3–0.8)	0.02

Table 4 Predictors of survival (multivariate analysis)

	Odds ratio (95% CI)	*P* value
Age	0.97 (0.9–1.1)	0.33
ECOG 1 vs 2	0.65 (0.4–1.1)	0.08
TI vs NO TI	0.2 (0.1–0.3)	0.0001
HMA vs LDAC	0.48 (0.29–0.79)	0.004
LDH	1.00 (0.9–1.2)	0.09
Blasts	1.00 (0.9–1.1)	0.68
Cytogenetic risk		
Good vs poor	1.1 (0.6–1.9)	0.6
Intermediate vs poor	1.4 (0.8–2.4)	0.1

ECOG eastern cooperative group performance status, *TI* transfusion independence, *LDH* lactated dehydrogenase, *HMA* hypomethylating agents, *LDAC* low-dose cytarabine

Table 5 Comparison of adverse events

	HMA (58)	LDAC (81)	*P* value
Neutropenia (grade 3–4)	40 (68.9%)	54 (65.4%)	0.54
Thrombocytopenia (grade 3–4)	38 (65.5%)	62 (76.5%)	0.13
Febrile neutopenia episodes	32	21	0.01
Bleeding	9 (15.3%)	20 (24.6%)	0.11
Infectious complications			
Sepsis	14 (24.1%)	12 (14.8%)	0.10
Pneumonia	12 (20.6%)	10 (12.3%)	0.53

Overall response rate did not differ between LDAC and HMA group; however, HMA cohort had a higher complete response and stable disease. About 46% of the overall patients and two-thirds of the patients with stable disease in HMA cohort achieved transfusion independence. Our observations were in agreement with the response rates and TI documented in the literature [8, 25].

LDAC/HMA prolonged survival compared to best supportive care. In our study, median survival was longer with HMA (6.4 months vs 3.9 months, $p = 0.00007$), in line with the previous studies [25, 26]. However, survival of our patients in both the cohorts (LDAC and HMA) was lower compared to randomized patients, likely because of irregular follow-up and inadequate supportive care. Similar experience is reported by Thepot et al. [27] and Ramos et al. [28], in the studies done in the real-world setting.

In the univariate analysis comparing HMA and LDAC cohorts, survival was longer with HMAs in patients with stable disease. Our observation reinforces that achieving stable disease with HMA increases the survival, was in accordance with the earlier studies [29]. Hence, stable disease with HMA should be considered; response and treatment should be continued until overt progression; nevertheless, there was no difference in survival in patients who had the response (ORR). Of note, HMAs compared to LDAC improved survival in patients with ECOG-2 performance status, likely due to higher and early responses/stable disease associated with HMA which improve the performance status. HMA improved survival in patients < 70 years; however, there was no difference in patients over 70 years, likely due to lower number of patients in this cohort and majority of them had succumbed to the disease. HMAs were effective than LDAC irrespective of cytogenetic risk and percentage of blasts. HMA effectiveness in increasing the survival of the patients with poor cytogenetics and higher blast percentage indicate that these agents can overcome the therapy resistance. These observations were consistent with the data from the clinical and preclinical studies in the literature [6, 8, 25]. Interestingly, survival of the patients with TI did not differ, indicating that the TI achieved with LDAC was of similar quality to that of HMA which was in contrast to the results from the post hoc analysis of AZA-AML-001 trial, where TI with CCR had no effect on survival [29].

In the mulitivariate analysis performed for the entire cohort, HMA treatment (HR = 0.48; 95% 0.29–0.79, $p = 0.004$) and transfusion independence (HR = 0.2; 95% 0.1–0.3, $p = 0.0001$) were independent predictors of survival, in accordance with the previous studies [25, 26, 29]. Neutropenia and febrile neutropenia were frequent in HMA cohort. LDAC patients had higher incidence of thrombocytopenia. Early deaths in HMA cohort are due to treatment-related complications as it is known that the complications are frequent in the first two cycles [30]. Disease progression was the major cause of early death in LDAC group. Inpatient admission rates were similar in both the groups, probably because of higher infectious complications in HMA group in contrast to RCTs reporting lesser inpatient days with HMA probably because of higher febrile neutropenia with HMA [25].

Our study being a retrospective in design has several limitations, confounding factors like heterogeneous patient and disease characteristics; treatment decisions made upon the various non-disease factors may affect the final outcome; hence, results should be interpreted cautiously. However, our study shows the real-world benefit of hypomethylating agents in elderly AML patients and brings forth the challenges of treating these patients in a resource-constrained setting.

Conclusion

Hypomethylating agents are effective in elderly AML patients compared to low-dose cytarabine, in the real-world context. Attaining transfusion independence and achieving a response or even stable disease improve survival. Universal health net is the needed and cost-effective newer therapies to improve the outlook of elderly AML patients in developing countries.

Compliance with ethical standards

The study was approved by the local ethics committee. Consent was obtained from all the patients before the treatment.

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

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