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Low-Dose Cytarabine versus Best Supportive Care for Patients with Acute Myeloid Leukaemia Unfit for the Standard of Care: Egyptian Centre Experience

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Abstract

Background: Acute myeloid leukaemia (AML) in the elderly is not strong enough to tolerate aggressive chemotherapy. We conducted the present study to compare the efficacy and safety of low-dose cytarabine (LDAC) with best supportive care (BSC) in Egyptian patients.

Method: A prospective randomized study included 60 eligible patients aged over 60 years with newly diagnosed AML. They were randomized to receive LDAC or BSC. The overall survival (OS) was the primary endpoint while the secondary endpoint was to compare the quality of life in the form of a length of hospital stays (LOHS), mode and frequency of admission in the two studied groups.

Results: Herein, 30 patients received LDAC and 30 patients received BSC. The mean survival time was 7.5 months in the BSC group compared to 10.2 months in the LDAC group. Even though the median OS was 8.4 months in the BSC group, it did not reach in the LDAC group; HR, = 2.047, CI 95% (0.541-7.743), (P=0.2).

There was a statistically significant association with LDAC and the frequency of hospital admission through the emergency department (ED) due to neutropenic fever and prolonged LOHS (P<0.001, P<0.002, and P<0.001, respectively).

Meanwhile, the admission through the outpatient clinic (OPC) and for transfusion support were statistically insignificant in the two groups (P< 0.12, P< 0.6, respectively).

Conclusion: Despite, there were no OS statistically significant benefits of the use of LDAC over BSC in our patients, poor quality of life in the form of frequent admission through the ED, more incidence of neutropenic fever, and prolonged LOHS were reported more to patients received LDAC.

Keywords: Leukemia, Myeloid, Acute, Best supportive care, Elderly, Low-dose cytarabine

Introduction

Acute myeloid leukaemia (AML) is believed to be a heterogeneous, highly aggressive, and hard-to-treat hematologic malignancy. Its risk of incidence increases with age. The median age is approximately 67 years and about one-third is over 75 years.[1]

In Egypt, the total number of newly diagnosed adult AML in the period from 2002-2010 was 1285, which represented approximately 17 % of the newly diagnosed adult leukemia.[2]

Despite recent progress of the diagnosis and treatment modalities, the prognosis of AML among older patients remains poor. Elderly AML is an incurable disease with a 2-year OS which is less than 10%. A minority of the elderly is eligible for aggressive treatment. This dismal prognosis may be related to the associated multiple co-morbidities that increase the probability of morbidity/mortality as well as the aggressive biological features. Accordingly, the management of the disease represents a worthy challenge.[3]

Therefore, these subtypes of patients may be treated with low-strength medication that may keep the patients in remission with only 20% median survival in less than one year.[4]

The standard care for elderly AML included low-intensity therapy (decitabine, 5-azacytadine, LDAC, gemtuzumab ozogamicin for CD33-positive, enasidenib for isocitrate dehydrogenase-2 mutation, ivosidenib for isocitrate dehydrogenase-1 mutation, and BSC.[5] In our center, these medications are not available, only we use low-dose cytarabine.

The current study aimed to compare the efficacy and the safety of LDAC with BSC in elderly AML unfit for the standard of care in our center.

Patients and methods

Patients

Newly diagnosed AML (>20% blasts) in the Medical Oncology Department, Zagazig University Hospital, aged over 60 years with Eastern Cooperative Oncology Group performance status (ECOG PS) score is ≤ 2 were included in the research. Likewise, secondary AML cases were enrolled. The exclusion criteria comprised patients with relapsed/refractory AML and previous usage of chemotherapy (except hydroxyurea).

Ethical approval to conduct the study was taken from the IRB Review Committee before the commencement of the study.

Pre-treatments work-up

Before starting the treatment, we performed clinical assessments, biochemical profile, complete blood count (CBC), bone marrow aspiration (BM), flow cytometry, and cardiac rhythm evaluation utilizing an electrocardiogram.

Study design and treatment protocol

This is a prospective randomized study conducted from March 2017 to June 2019, which compared LDAC vs BSC in the treatment of elderly AML. Written informed consent was received from all the eligible patients.

LDAC was administered at 10mg/m2 twice per day subcutaneously for 10 days every 4 weeks. (The primary physician or the main caregiver was responsible for drug administration).

The therapy continued until death or unacceptable toxicity. The treatment stopped once we faced febrile neutropenia (oral temperature >38.5°C with an absolute neutrophil count <0.5×109/l), hemorrhage with platelet <25.000/l, impaired hepatic or renal functions. For the evaluation of the results, BM aspiration was requested if CBC normalized without blasts in peripheral blood or prolonged cytopenia more than 4 weeks to decide whether that cytopenia was due to the persistence of the disease or therapy-induced myelosuppression.

The primary endpoint of our study was the median OS; defined as the time from diagnosis to death or the last follow-up and the secondary endpoint was the comparison of the quality of life regarding

the length of hospital stays (LOHS), mode and frequency of hospital admission in the two groups.

Statistical analysis

Continuous variables were expressed as the mean ± SD and the median (range) and categorical variables were expressed as a number (percentage). The continuous variables were checked for normality using a Shapiro-Wilk test. The Mann-Whitney U test was employed to compare the two groups concerning the non-normally distributed variables. The percentage of categorical variables was compared using whether Pearson's Chi-square test or Fisher's exact test. The OS was calculated as the time from randomization to death or the most recent follow-up contact (censored). These time-to-event distributions were calculated employing the method of Kaplan-Meier plot. They were then compared using a two-sided exact log-rank test. Univariate Cox regression was used to estimate hazard ratios and its corresponding Wald 95%CI (confidence interval). All the tests were two-sided. A $P<0.05$ was considered to be significant. All the statistics were performed with SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA).

Results

A total of 60 patients were eligible, among whom 30 received LDAC and 30 received BSC. The demographic and clinical features were comparable in the two groups (Table 1). 50% of the patients were male in the LDAC group compared with 43.3% in the BSC group. The median age, types of AML, and the ECOG PS score were almost equally distributed.

Considering the admission features along with the LDAC group, the majority (66%) of the patients visited and admitted to inpatient services through ED due to the neutropenic fever was statistically significant compared with the BSC group ($P<0.002$). Moreover, the patients on LDAC experienced LOHS ($P<0.001$) (Table 2).

The survival analysis revealed that the mean survival time was 7.5 months in the BSC group compared with 10.2 months in the LDAC group. The median OS was 8.4 months in the BSC group whereas it was not reached in the LDAC group, which was statistically insignificant; HR (CI 95%) = 2.047 (0.541-7.743), ($P = 0.279$). (Table 3 and Figure1).

Discussion

In the current study, we compared LDAC with BSC in newly diagnosed elderly AML. There was a numerical improvement in the mean survival time of the LDAC group compared to that in the BSC group. The median OS was not reached in the LDAC group compared with 8.4 months in the BSC group. The non-reachable OS might be explained by the nature of the disease is aggressive and incurable with poor outcome.

This finding was not matching that of previous studies which reported that the median OS ranged from 3.2 months to 10.1months in newly diagnosed elderly AML treated with LDAC.[6-12]

Heiblig et al. published their experiences regarding LDAC in elderly AML (≥ 70 years old) and compared the results of those of BSC. Median OS was 9.6 months and 3.4 months ($P=0.001$) for the LDAC group and the BSC group, respectively.[13]

A multi-center, randomized, open-label study, which involved 448 patients aged over 65 years with newly diagnosed AML evaluated the conventional care options (included BSC) versus azacitidine. The median OS was reported to be 6.5 months and 10.4 months, respectively in the two groups. [14]

A pilot study carried out on 15 elderly patients with newly diagnosed AML showed that OS was 5.5 months in the LDAC group.[15]

The variation in the results may be attributed to the demographic and clinical features of our patients. The median age of our patients were younger (64.0, range: 60-7) and there was no risk classification,

either cytogenetic or molecular, due to financial aspects. Moreover, the Egyptian patients might have specific genetic, etiologic, or biological factors that could lead to different pharmacokinetics, tolerance, or efficacy of the therapy.

In the current study, patients who received LDAC suffered from frequent hospital admission through the ED, more incidence of neutropenic fever, and prolonged LOHS in comparison with patients in the BSC group (P<0.001, P=0.002, and P<0.001, respectively), which was statistically significant. In contrast, there was no statistical significance of hospital admission through the OPC or due to transfusion support (P= 0.12, and P<0.6, respectively).

The choice of treatment protocol depends on patient-related factors, disease features, social support, and patient wishes. A recent report from the Surveillance, Epidemiology, and End Results Program reported that only 40% of elderly AML received specific anti-cancer directed therapy. Furthermore, it is not necessary to treat all patients; it should be based on risk-benefit criteria.[16]

In certain developing countries, such as Egypt, newly approved medications for the treatment of AML among the elderly who are not candidates for intensive remission induction therapy are not available in all oncology centers. Thus, LDAC and BSC are the only two options of treatment in our hands, which could be employed in the treatment of those subtypes of patients.

Furthermore, we have patients with a low socioeconomic level, incurable diseases, and poor ECOG PS, which preclude the use of the standard of care. Treating these patients with LDAC, despite the numerical improvement in the rate of survival, it resulted in worse quality of life.

Limitations

The current work was not without limitations. Primarily, the sample size was small, which might affect the reliability of the results. Additionally, although the National Comprehensive Cancer Network (NCCN) has determined certain treatment guidelines mainly dependent on the assessment of cytogenetic or molecular features, they were not followed in our study.

Conclusion

Concerning the treatment of Egyptian elderly AML, no statistically significant benefits were observed using LDAC over BSC. Moreover, it resulted in poor quality of life in the form of frequent admission through the ED, more incidence of neutropenic fever, and prolonged LOHS. The cause of poor tolerance was not identified; however, it may be related to different genetic, etiologic, or biological factors. A considerable number of patients in Egypt suffering from cancer had a low socioeconomic level. Hence, if no improvement is achieved in the disease outcome or quality of life of cancer-directed therapy, there is no need to increase patients suffering. The BSC was observed to be a good option of the treatment of Egyptian elderly AML.

Conflict of Interest

None declared.

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. Zawam H, Salama R, Alsirafy SA, Bishr MK. Treatment outcome of acute myeloid leukemia in Egypt: A developing country perspective. *Int J Cancer Treat.* 2018:53-9.
3. Juliusson G, Antunovic P, Derolf A, Lehmann S, Möllgård L, Stockelberg D, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood.*

2009;113(18):4179-87. doi: 10.1182/blood-2008-07-172007.
4. Almeida AM, Ramos F. Acute myeloid leukemia in the older adults. *Leuk Res Rep.* 2016;6:1-7. doi: 10.1016/j.lrr.2016.06.001.
5. Klepin HD, Estey E, Kadia T. More versus less therapy for older adults with acute myeloid leukemia: New perspectives on an old debate. *Am Soc Clin Oncol Educ Book.* 2019; 39:421-32. doi: 10.1200/EDBK_239097.
6. Döhner H, Seymour JF, Butrym A, Wierzbowska A., Selleslag D, Jang JH et al. Overall survival in older patients with newly diagnosed acute myeloid leukemia (AML) with > 30% bone marrow blasts treated with azacitidine by cytogenetic risk status: results of the AZA-AML-001 study. Blood. 2014;124(21):621.
7. Baccarani M, Tura S. Differentiation of myeloid leukaemic cells: new possibilities for therapy. *Br J Haematol.* 1979;42(3):485-7.
8. Kumar L, Kochupillai V, Dua H. Low-dose cytosine arabinoside in acute non-lymphoblastic leukemia. *Cancer.* 1989;63(3):415-8.
9. Housset M, Daniel MT, Degos L. Small doses of ARA-C in the treatment of acute myeloid leukaemia: differentiation of myeloid leukaemia cells? *Br J Haematol.* 1982;51(1):125-9.
10. Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol.* 2012;30(21):2670-7. doi: 10.1200/JCO.2011.38.9429.
11. Bashir Y, Geelani S, Bashir N, Mir SA, Mushtaq M, Jan MA, et al. Role of low dose cytarabine in elderly patients with acute myeloid leukemia: An experience. *South Asian J Cancer.* 2015;4(1):4-6. doi: 10.4103/2278-330X.149918.
12. Weh HJ, Zschaber R, von Paleske A, Hossfeld DK. Treatment of acute myeloid leukemia and myelodysplastic syndrome by low dose cytosine arabinoside. *Haematol Blood Transfus.* 1985;29:60-2.
13. Heiblig M, Elhamri M, Tigaud I, Plesa A, Barraco F, Labussière H, et al. Treatment with low-dose cytarabine in elderly patients (age 70 years or older) with acute myeloid leukemia: A single institution experience. *Mediterr J Hematol Infect Dis.* 2016;8(1):e2016009. doi: 10.4084/MJHID.2016.009.
14. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood.* 2015;126(3):291-9. doi: 10.1182/blood-2015-01-621664.
15. Jacob LA, Aparna S, Lakshmaiah KC, Lokanatha D, Babu G, Babu S, et al. Decitabine compared with low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia: A pilot study of safety, efficacy, and cost-effectiveness. *Adv Hematol.* 2015;2015:167029. doi: 10.1155/2015/167029.
16. Medeiros BC, Satram-Hoang S, Hurst D, Hoang KQ, Momin F, Reyes C. Big data analysis of treatment patterns and outcomes among elderly acute myeloid

leukemia patients in the United States. *Ann Hematol.* 2015;94(7):1127-38. doi: 10.1007/s00277-015-2351-x.

Table 1. Demographic and clinical features of two groups

Characteristics	**LDAC N=30** **No** **%**	**BSC N=30** **No** **%**	***P* value**
Age (years)			
Mean± SD	64.96±3.27	64.90±3.98	0.8
Median (Range)	64.0(60-71)	64.5(61-71)	
Sex			
Male	15	13	0.6
Female	50	43.3	
	15	17	
	50	56.7	
PS Score			
1	12	12	1.0
2	40	40	
	18	18	
	60	60	
Types of AML			
Primary	26	27	1.0
Secondary	86.7	90	
	4	3	
	13.3	10	

LDAC: Low-Dose Cytarabine; BSC: Best supportive care; PS: Eastern Cooperative Oncology Group (ECOG) Performance Status; AML: Acute myeloid leukaemia.

Table 2. Comparison of admissions characteristics

Characteristics	LDAC N=30 No %	BSC N=30 No %	*P* value
Admission through OPC			
Mean± SD	1.1±0.402	1.3±0.479	
Median (Range)	1.0(0.00-2.00)	1.0(1.00-2.00)	
Admission frequency:			
1	25	20	0.12
=2	83.3	66.7	
Admission through ED	4	10	
Mean± SD	16.7	33.3	
Median (Range)			
Admission frequency	2.03±0.927	1.0±0.454	
1	2.0(1.00-4.00)	1.0(0.00-2.00)	
=2			<0.001
3-4	10	27	
	33.3	90	
	11	3	
	36.7	10	
	9	0	
	30.0	0.0	
Causes of admission			
Transfusion support	1.267±0.639	1.16±0.647	0.6
Mean± SD	1.0(0.00-3.00)	1.0(0.00-2.00)	
Median (Range)			
Neutropenic fever			
Mean± SD	1.87±0.860	1.23±0.568	0.002
Median (Range)	2.0(0.00-4.00)	1.0(0.00-2.00)	
LOHS (days)			
Mean± SD	74.23±21.356	55.36±14.655	<0.001
Median (Range)	68.0(35.0-125.0)	53.0(33.0-88.0)	

LDAC: Low-Dose Cytarabine; BSC: Best supportive care; OPC: out patients' clinic; ED: Emergency Department; LOHS: length of stay

Table 3. Comparison of outcomes in the two groups

Characteristics	LDAC	BSC
Received cycles		
Median	4	0
Range	1-7	0
Overall Survival (Month)		
Mean survival time	10.2	7.5
Median	NR	8.4
Survival distribution		
Log-rank test, *P* value	**0.2**79	
Hazard ratio (95% confidence interval)	2.047(0.541-7.743)	

LDAC: Low-Dose Cytarabine; BSC: Best supportive care; NR: not reached

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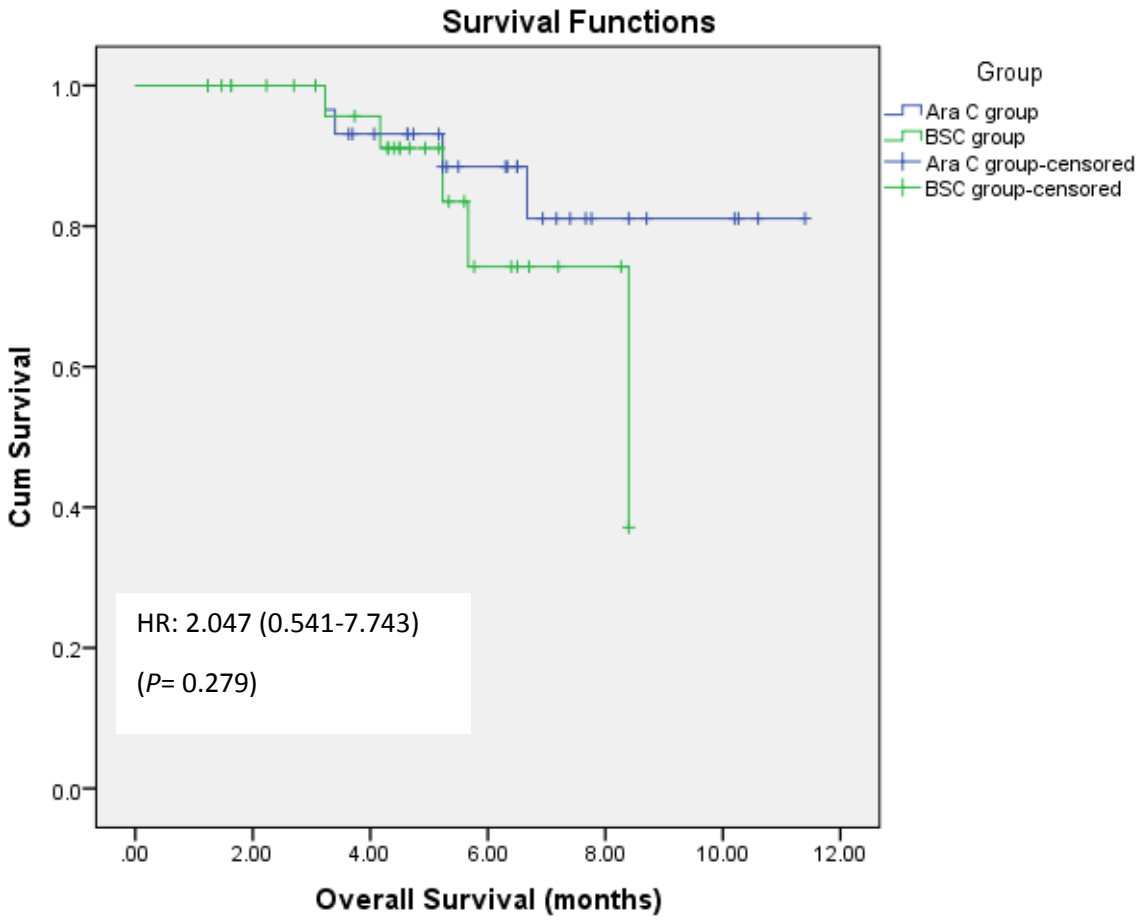

Figure 1. This figure represents the Kaplan-Meier survival curve compared low-dose cytarabine vs BSC.

LDAC: Low-Dose Cytarabine; BSC: Best supportive care.