Article published online: 2021-05-23

Original Article

Hypomethylating Agents Use in Acute Myeloid Leukemia: A Single-Center Experience

Sravan Kumar Bodepudi[1], Santhosh Kumar Devdas[1], Vinayak V Maka[1], Rasmi Palassery[1], Sumathi S Hiregoudar[2], Nalini Kilara[1]

[1]Department of Medical Oncology, Ramaiah Medical College, Bengaluru, Karnataka, India, [2]Transfusion Medicine and Blood Centre, Ramaiah Medical College, Bengaluru, Karnataka, India

Abstract

Context: Acute myeloid leukemia (AML) is a heterogeneous disease. Approximately 80% of older AML patients will die of their disease or its treatment with currently available antileukemic therapy because of the adverse prognostic risk factors. In elderly patients who are not candidates for induction chemotherapy (IC) or who declines IC, the preferred induction regimen is with hypomethylating agents (HMAs). In India, data regarding therapy with HMA, response to therapy and overall survival (OS) is seldom reported. **Aims:** This study aims to study the response rate and survival of patients treated with HMAs in whom IC was not feasible. **Settings and Design:** This is retrospective and descriptive single-center study. **Subjects and Methods:** Data of newly diagnosed AML patients who were unfit for IC and treated with HMA in our institution was collected retrospectively and analyzed. **Results:** Twenty-three patients received HMAs as a treatment for AML. Eight (34.7%) of 23 patients had initial response to therapy (two [25%] had complete remission [CR], four [50%] had CR with incomplete hematologic recovery, one [12.5%] had partial remission) and one (12.5%) had stable disease. The median progression-free survival and OS observed are 6.06 ± 0.65 months and 7 ± 1.32 months, respectively.**Conclusions:** HMAs provide an important additional treatment option in newly diagnosed AML patients who are older, with poor performance status, higher comorbidity indices, and who refuse IC.

Keywords: *Hypomethylating agents, induction chemotherapy, performance status*

Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by infiltration of the bone marrow (BM), blood, and other tissues by mutated clonal hematopoietic progenitor cells and abnormal differentiation of hematopoietic lineages, ultimately leading to marrow failure.[1,2] The incidence of AML increases with advancing age, with half of the new cases diagnosed in adults aged ≥65 years. Approximately 80% of older AML patients will die of their disease or its treatment with currently available antileukemic therapy because of the adverse prognostic risk factors, such as history of myelodysplastic syndromes (MDSs), unfavorable karyotypes, poor performance status (PS), and comorbidities associated with aging, which can limit treatment options.[3] As a result, many older patients receive only palliative care. Median overall survival (OS) of AML patients ≥65 years of age is only 2–8 months.

Commonly used therapeutic options to treat older patients with AML are the best supportive care alone, standard induction chemotherapy (IC), and low-dose cytarabine arabinoside (LDAC). Fitness for IC is decided based on factors such as age, PS, functional status, and comorbid conditions. The National Comprehensive Cancer Network guidelines recommend IC for fit patients with age ≥60 years. However, many older patients with AML do not meet the fitness criteria. In elderly patients, who are not candidates for IC or who declines IC, the preferred induction regimen is with low intensity azacitidine (AZA) or decitabine (DAC).[4]

Epigenetic changes are heritable changes in gene expression that are not caused by changes in the primary DNA sequence, and they affect the spatial structure of the DNA that is coiled around histones. This spatial structure determines binding of transcription machinery to the promoter of a gene, in order to initiate transcription.[5] Methylation and acetylation of amino acid residues in histones and

How to cite this article: Bodepudi SK, Devdas SK, Maka VV, Palassery R, Hiregoudar SS, Kilara N. Hypomethylating agents use in acute myeloid leukemia: A single-center experience. Indian J Med Paediatr 2020;41:202-8.

Submitted: 18-Jul-2019
Revised: 14-Oct-2019
Accepted: 29-Dec-2019
Published: 13-Jun-2020

Address for correspondence:
Dr. Santhosh Kumar Devdas, Department of Medical Oncology, Ramaiah Medical College, MSR Nagar, MSRIT Post, Bengaluru - 560054, Karnataka, India.
E-mail: drsanthoshkumar28@gmail.com

Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_155_19

Quick Response Code:

methylation of cytosine (C) bases in areas of the genome rich in CpG dinucleotides (CpG islands) are the best-known epigenetic changes. Cancer cells exhibit genome-wide hypomethylation, resulting in genetic instability, and CpG islands hypermethylation which modifies gene expression.[6] Epigenetic changes are reversible, making them an attractive target for therapeutic intervention.

Abnormal methylation plays an important role in the pathogenesis of AML. Genes such as DNA-methyltransferase-3A *(DNMT3A)*, Ten-Eleven-Translocation-2, and isocitrate dehydrogenase-1 and 2 are involved in DNA methylation, and their mutated variants may help interpret the mechanisms of aberrant DNA methylation in AML blasts.[2]

Hypomethylating agents

Five-azacytidine (AZA) and 5-aza-2′-deoxycytidine (DAC) were synthesized as analogs of C for the treatment of AML in 1960s. They were extremely toxic at higher antineoplastic doses and hence were phased out. Discovery of hypomethylating properties of these drugs renewed interest in their clinical use. They act as DNMT inhibitors, leading to global hypomethylation of C residues associated with gene expression control.[7]

In India, data regarding therapy with HMA, response to therapy and overall survival (OS) is seldom reported. The objective of this retrospective study was to study the response rate and survival of patients treated with HMAs in whom IC was not feasible.

Subjects and Methods

This is a retrospective and descriptive single-center study. All patients with a diagnosis of AML who presented to the Department of Medical Oncology at our institution and received HMAs (AZA and DAC) were enrolled. The patient's demographic data, Eastern Cooperative Oncology Group (ECOG) PS, comorbidities, and baseline investigations were collected. Charlson comorbidity index (CI),[8] hematopoietic cell transplantation (HCT) CI[9] were calculated.

Treatment regimen

AZA was administered at 75 mg/m^2/day for 7 days intravenous (IV) repeated every 28-day and DAC was administered at 20 mg/m^2/day for 5 days, IV repeated in a 28-day at physician's discretion. Therapy was continued until progressive disease (PD) or toxicity in patients with partial remission (PR) or hematologic improvement.

Response rates

Criteria developed by the International Working Group (IWG) were used to define response rates such as complete remission (CR), CR with incomplete hematologic recovery (CR$_i$), PR, and stable disease, PD.[10,11]

Transfusion independence

Transfusion independence was defined as a transfusion-free period of 3 months after treatment assignment. Transfusion dependence at baseline was defined as two or more transfusions per month within 90 days before the assignment.[12]

Statistical methods

All the numerical characteristics such as age and duration of disease were discussed through the descriptive statistics in terms of mean and standard deviation or median and interquartile range. Qualitative variables were described as percentages. OS was calculated from the date of treatment initiation to the date of death. The analysis was performed using IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. (Armonk, NY: IBM Corp.).

Results

Twenty-three patients received HMAs as treatment for AML (12 patients received DAC and 11 patients received AZA). The patient characteristics are summarized in Table 1. The median age was 62 years, ranging from 34 to 78 years. Patients included in this analysis were deemed unfit for IC in view of advanced age, comorbidities, poor PS, or financial constraints. There were 11 male patients and 12 female patients. ECOG PS was 1 in 4 patients and ≥2 in 19 patients. HCT-CI was ≤2 in 16 patients and ≥3 in 7 patients. Charlson CI was ≤5 in 19 patients and ≥6 in 4 patients. One patient received prior therapy with LDAC and two patients received IC. Three patients had antecedent MDS.

Median hemoglobin (Hb) was 7.8 g/dl (range 6.7–11.4). The median white blood cell (WBC) count was 6.2 × 10^3/μL (range 0.68–159). Median platelet count was 0.42 × 10^5/μL (0.02–3.74). Four patients (18%) had BM blasts <30% and nineteen patients (82%) had > 30%, respectively, and median BM blast count was 59% (range 8–95). The 2017 European Leukemia Net risk stratification of AML by genetics was used to risk stratify patients. Cytogenetics were available in 17 patients (74%). Seven patients (30.4%) had intermediate-risk and eight patients (34.8%) had poor-risk cytogenetics. Molecular studies were available only in eight patients (34.8%). Two patients (8.7%) had mutated FLT3-ITD and one patient (4.3%) had mutated nucleophosmin with FLT3-ITD. Five patients had no detected mutations. Median dose/day was 100 mg (range 100–149) for AZA and 32 mg (range 25–40) for DAC.

Response to therapy

Only eight patients received three or more cycles of HMAs. Fifteen patients received <3 cycles because of early death in 11 patients, PD in 4 patients. Initial response (including CR/CRi/PR according to IWG) was evaluated after three cycles. Among patients who received three cycles of therapy, seven (87.5%) patients had response to therapy, (two [25%]

Table 1: Patient characteristics

Demographics	Patients, *n* (%)
Sex	
Male	11 (47.8)
Female	12 (52.2)
Median age (years) (range)	62 (34-78)
ECOG PS	
0	0
1	4 (17.4)
2	8 (34.7)
3	10 (43.4)
4	1 (4.3)
Comorbidities	
Type II DM	9 (39.1)
HTN	7 (30.4)
Renal disease	4 (17.4)
Infections	6 (26.1)
HCT-CI	
0	6 (26.1)
1-2	10 (43.4)
≥3	7 (30.5)
Charlson CI	
0-3	4 (17.4)
4-5	15 (65.2)
≥6	4 (17.4)
Previous therapy	
Nil	20 (86.9)
LDAC	1 (4.3)
IC	2 (08.7)
Antecedent MDS	3 (13)
Hb	
Median	7.8 (6.7-11.4)
<10	21 (91.3)
≥10	2 (8.7)
WBC	
Median×10^3/μL	6.2 (0.68-159)
<5000	11 (47.8)
5000-50,000	7 (30.4)
>50,000	5 (21.8)
Platelet count	
Median×10^5/μL	0.42 (0.02-3.74)
<50,000	13 (56.5)
≥50,000	10 (43.5)
BM blasts percentage	
Median	59 (8-95)
<30	4 (17.4)
30-50	5 (21.8)
>50	13 (56.5)
Missing	1 (04.3)
Cytogenetics	
Missing	6 (26)
Favorable	2 (8.7)
Intermediate	7 (30.4)
Adverse	8 (34.8)
Molecular features	
FLT3-ITD	2 (8.7)
NPM1/FLT3-ITD	1 (4.3)
Negative	5 (21.7)
Missing	15 (65.3)

ECOG – Eastern Cooperative Oncology Group; PS – Performance status; DM – Diabetes mellitus; HTN – Hypertension; HCT – Hematopoietic cell transplantation; CI – Comorbidity index; LDAC – Low-dose cytarabine arabinoside; IC – Induction chemotherapy; MDS – Myelodysplastic syndrome; WBC – White blood cell; Hb – Hemoglobin; BM – Bone marrow

had CR, four [50%] had CRi, one [12.5%] had PR) and one (12.5%) had stable disease [Table 2]. One patient who achieved CR after three cycles of AZA therapy received IC with high-dose cytarabine (HIDAC). Post-HIDAC, he had PD and was restarted on AZA. He had PR with AZA and received a total of 9 cycles after which he had PD. One patient achieved CRi after 3 cycles of DAC therapy and remained in CRi till 8 cycles. He developed cytopenia and had 8% BM blasts after, continued to receive DAC therapy for 18 cycles at the time of this publication and remained in PR.

Median progression-free survival (PFS) was 8 ± 2.39 weeks and median OS was 10 ± 5.29 weeks [Figure 1]. Among patients, who received at least three cycles of therapy, the median PFS was 26 ± 2.82 weeks and median OS was 30 ± 5.66 weeks [Figure 2].

Among eight patients who responded to therapy, eight patients (100%) were <65 years of age, five patients (62.5%) had PS <3, six patients (75%) had HCT-CI <3, seven patients (87.5%) had Charlson CI <6, six patients (75%) had WBC counts <50,000/cumm, six patients (75%) had blasts more than 30%, and six patients (75%) had intermediate- or poor-risk cytogenetics, cytogenetics was not available in the other two patients.

In univariate analysis [Table 3], one of the 10 variables was found to have association with response to HMA therapy. Patients with the age <65 years had good response to therapy. Cytogenetics, PS, blasts percentage, WBC counts, Hb, platelet count, sex, and HCT-CI had no significant impact on response to therapy.

None of the variables had a significant impact on response to therapy in the multivariate analysis. Transfusion independence was noted in three patients. Two patients were transfusion independent after two cycles of therapy and one patient after four cycles of therapy.

Discussion

The management of AML in India remains a challenge. In a study conducted in CMC, Vellore, by Philip *et al*.[13] 271 (71.31%) of 380 newly diagnosed AML patients did

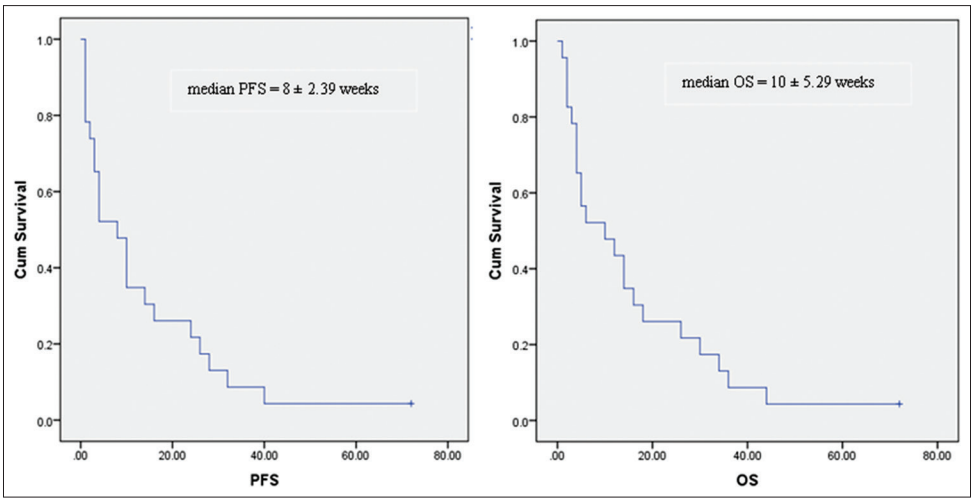

Figure 1: Median progression-free survival and overall survival among all patients

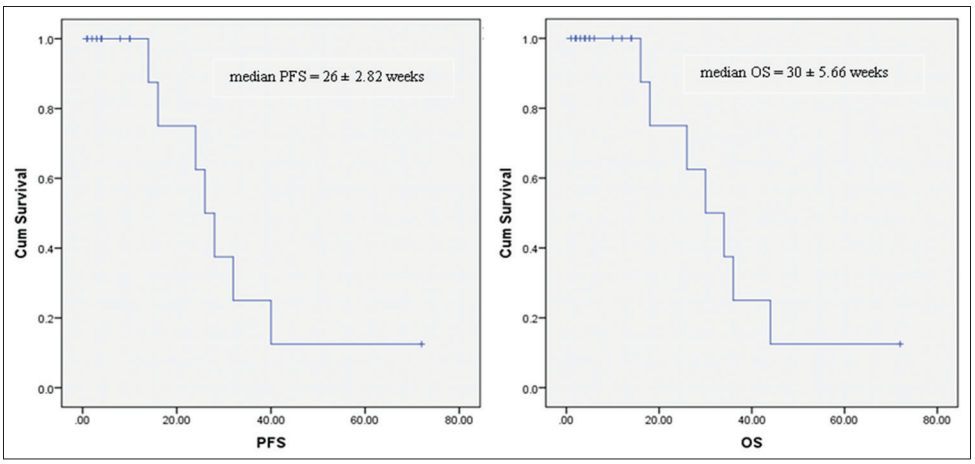

Figure 2: Median progression-free survival and overall survival in patients who received median three cycles of therapy

Table 2: Response at initial evaluation and best response

Response	After 3 cycles (%)	Best response (%)
Overall response	8 (34.7)	8 (34.7)
CR	2 (8.69)	3 (13)
CRi	4 (17.4)	4 (17.4)
PR	1 (4.35)	0
SD	1 (4.35)	1 (4.35)
Others[a]	15 (65.2)	15 (65.2)

[a]Patients who received <3 cycles of therapy. CR – Complete remission; CRi – CR with incomplete hematologic recovery; PR – Partial remission; SD – Stable disease

not receive standard of care. The main reasons for not receiving standard of care were financial constraints, poor PS and comorbidities. Treatment in AML patients with comorbidities, poor PS, advanced age, and financial constraints remain a challenge. In India, all patients do not receive standard of care with IC due to various reasons as discussed earlier.[13] Treatment with HMAs is a reasonable alternative in such individuals as HMAs are well tolerated with less adverse events when compared with IC. The efficacy of HMAs in the treatment of AML is well established based on many clinical trials [Table 4].

Azacitidine

Cancer and Leukemia Group B (CALGB) cooperative group evaluated the efficacy of HMAs in AML/MDS patients. Therapy with AZA in MDS resulted in response rates ranging from 30% to 60%, with documented improved survival.[14-16] In the phase 3 AZA-001 trial, older patients with 20%–30% BM blasts treated with AZA had prolonged OS compared with conventional care regimens (CCRs).[15] In the Austrian Azacitidine Registry[17,18] and French compassionate use program,[19] patients with AML treated with AZA had a median OS of approximately 9–10 months. AZA was approved for use in AML in 2004 in the USA based on the CALG 9221 trial.

Decitabine

Various dosing schedules of DAC had been studied in AML patients. The European organization for Treatment of Cancer cooperative group trial in MDS/AML patients using a DAC at 15 mg/m^2 dose every 8 h 3 days schedule resulted in

complete and PR rates of 26% with no difference between patients with or without adverse cytogenetics. The median OS was 5.5 months, 1-year survival and 2-year survival rates were 28% and 13%, respectively.[20] DACO-016 study compared the efficacy and safety of DAC (20 mg/m^2/day for 5 days every 4 weeks) versus treatment choice in 485 patients IC ineligible patients.[21] Planned primary analysis of this trial did not show a significant improvement of OS (median OS 7.7 months vs. 5.0 months), follow-up analysis was in favor of DAC. DAC was approved for the treatment of AML in Europe based on the data from this study.

In our retrospective study of 23 patients with AML, who were treated with HMAs, a response rate of 34.7% (including CR/Cri/PR) was observed. In a study of AZA in untreated AML by Thépot *et al*., the best response rate was 33%.[19] Our results are consistent with those reported in other studies.[21,22] AZA dose was capped at 100 mg/day in patients who had financial constraints. The median time to best response was 136 days.

All the patients who had response to therapy were younger than 65 years of age. In our study, younger patients were offered HMA in view of ineligibility for IC regimens due to various reasons as stated earlier. Age <65 years had a significant impact on the response to therapy. Patients with higher comorbidity indices (HCT-CI >2, Charlson CI > 5) did not have good response to therapy in our study, indicating that comorbidities have a significant impact on response and survival in AML patients treated with HMAs.

Hb level, platelet counts, and WBC did not have an impact on response to therapy in our trial. However, in patients who presented with leukopenia had a nonsignificant trend toward worse outcomes (odds ratio - 1.42, 95% confidence interval 0.51–3.91). AZA therapy prolonged OS compared with CCRs in older patients with 20%–30% BM blasts in the phase 3 AZA-001 trial.[15] The same results could not be established in our study as the patient population with blasts <30% is very small (17%).

IC and LDAC provide no OS benefit in older patients with AML and poor cytogenetics, and in such patients, HMA therapy provides better outcomes.[23-25] In our study, patients cytogenetic risk had no impact on response to therapy. This can be attributed to the nonavailability of risk stratification in all patients and small sample size.

The median PFS and OS observed in our study are 6.06 ± 0.65 months and 7 ± 1.32 months, respectively, for patients who received a minimum of three cycles

Table 3: Univariate analysis for response to therapy

	Response	
	OR (95% confidence interval)	***P***
Age (<65 years)	0.53 (0.33-0.85)	0.021
Sex (male/female)	0.87 (0.15-4.87)	0.87
ECOG PS (0-1/2+)	0.22 (0.03-1.49)	0.11
HCT-CI (>2)	3.2 (0.46-22.16)	0.26
Charlson CI (>6)	0.73 (0.54-0.99)	0.10
Hb (>10 g/dl)	0.87 (0.71-1.05)	0.28
WBC (≥15,000)	0.8 (0.53-2.69)	0.65
Platelet count	0.68 (0.12-3.96)	0.67
Blasts (>30%)	1.06 (0.64-1.71)	0.78
Cytogenetics	0.83 (0.64-1.07)	0.33

ECOG – Eastern Cooperative Oncology Group; PS – Performance status; HCT – Hematopoietic cell transplantation; CI – Comorbidity index; WBC – White blood cell; Hb – Hemoglobin; OR – Odds ratio

Table 4: Acute myeloid leukemia trials and subset analysis of acute myeloid leukemia (20%-30% bone marrow blasts) in myelodysplastic syndrome trials

Reference	AML type	Median age (years)	Drug dose and schedule	Patients, *n*	CR/PR (%)	ORR[a] (%)	Median OS (months)
Silverman 2006[16]							
CALGB 8421	AML (20%-30% BM blasts)	65	AZA, 75 mg/m^2/day, for 7 days, IV	25	4 (12)	12 (48)	–
CALGB 9221		69	Two randomization arms				
			AZA, 75 mg/m^2/day for 7 days, SQ	27	2 (7)	10 (37)	19.3
			BSC	25b	0 (0)	2 (8)[b]	12.9
Fenaux 2010[15]	AML (20%-30% BM blasts)	70	Two randomization arms				
			AZA, 75 mg/m^2/day for 7 days, SQ	55	10 (18)[c]		24.5
			BSC, LDAC, or ICT	58	9 (16)[c]		16
Lubbert 2012[20]	WHO AML	72	DAC 15 mg/m^2/8 h for 3 days, IV	227	59 (26)[d]	-	5.5
Kantarjian 2012[21]	WHO AML	73	DAC 20 mg/m^2/day, for 5 days, IV	242	44 (18)	73 (30)	7.7
			BSC or LDAC	243	27 (11)	34 (14)	5
Dombret 2015[27]	WHO AML[e]	75	AZA, 75 mg/m^2/day for 7 days, SQ	231	50 (22)	70 (30)	10.4
			BSC, LDAC, or ICT	247	57 (23)	65 (26)	6.5

[a]ORR, including CR/PR, CRi, and/or hematological improvements; [b]13 patients received study drug after crossover; [c]CR only; [d]PR criteria used in this study, included patients with persistent cytopenia; [e]If >30% marrow blasts and WBC <15 G/L. BM – Bone marrow; BSC – Best supportive care; DAC – Decitabine; LDAC – Low-dose *cytarabine arabinoside*; ICT – Intensive chemotherapy; AML – Acute myeloid leukemia; CR – Complete remission; PR – Partial remission; AZA – Azacitidine; IV – Intravenous; ORR – Overall response rate; OS – Overall survival; WBC – White blood cell; CRi – CR with incomplete hematologic recovery; SQ – Subcutaneous

of therapy. In a multicenter DAC phase II trial in 227 older AML patients, CR/PR rate was 26% and median OS was 5.5 months.[26] Our results are comparable with other studies.[17,19,22,27] When survival rates are evaluated in the entire study group, the median PFS and OS were 1.86 ± 0.55 months and 2.33 ± 1.23 months' respectively. The decrease in the survival rates can be attributed to early deaths in 15 (65%) patients. The incidence of adverse events could not be evaluated in the study group due to lack of documentation, as the study being a retrospective analysis.

Conclusion

AZA and DAC provide an important additional treatment option in newly diagnosed AML patients who are older, with poor PS, higher comorbidity indices and who refuse IC.

Acknowledgment

I would like to express my heartiest thanks to Dr. N. S. Murthy (Research Co-ordinator, Dept. of Research and Patents) for his guidance and timely help. I am very thankful to my colleagues, Dr. Mubarakunnisa and Dr. Sai Madhuri who stood by me throughout this work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med 2015;373:1136-52.
2. Cancer Genome Atlas Research Network, Ley TJ, Miller C, Ding L, Raphael BJ, Mungall AJ, *et al*. Genomic and epigenomic landscapes of adult *de novo* acute myeloid leukemia. N Engl J Med 2013;368:2059-74.
3. Dombret H, Gardin C. An update of current treatments for adult acute myeloid leukemia. Blood 2016;127:53-61.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Ver. 2. National Comprehensive Cancer Network; 2019. Available from: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. [Last accessed on 2019 Mar 27].
5. Grønbaek K, Hother C, Jones PA. Epigenetic changes in cancer. APMIS 2007;115:1039-59.
6. Jones PA, Baylin SB. The epigenomics of cancer. Cell 2007;128:683-92.
7. Jasielec J, Saloura V, Godley LA. The mechanistic role of DNA methylation in myeloid leukemogenesis. Leukemia 2014;28:1765-73.
8. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373-83.
9. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, *et al*. Hematopoietic cell transplantation (HCT)-specific comorbidity index: A new tool for risk assessment before allogeneic HCT. Blood 2005;106:2912-9.
10. Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, *et al*. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21:4642-9.
11. de Greef GE, van Putten WL, Boogaerts M, Huijgens PC, Verdonck LF, Vellenga E, *et al*. Criteria for defining a complete remission in acute myeloid leukaemia revisited. An analysis of patients treated in HOVON-SAKK co-operative group studies. Br J Haematol 2005;128:184-91.
12. Gale RP, Barosi G, Barbui T, Cervantes F, Dohner K, Dupriez B, *et al*. What are RBC-transfusion-dependence and-independence? Leuk Res 2011;35:8-11.
13. Philip C, George B, Ganapule A, Korula A, Jain P, Alex AA, *et al*. Acute myeloid leukaemia: Challenges and real world data from India. Br J Haematol 2015;170:110-7.
14. Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, *et al*. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: A study of the cancer and leukemia group B. J Clin Oncol 2002;20:2429-40.
15. Fenaux P, Mufti GJ, Hellström-Lindberg E, Santini V, Gattermann N, Germing U, *et al*. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol 2010;28:562-9.
16. Silverman LR, McKenzie DR, Peterson BL, Holland JF, Backstrom JT, Beach CL, *et al*. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: Studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 2006;24:3895-903.
17. Pleyer L, Stauder R, Burgstaller S, Schreder M, Tinchon C, Pfeilstocker M, *et al*. Azacitidine in patients with WHO-defined AML – Results of 155 patients from the Austrian Azacitidine Registry of the AGMT-Study Group. J Hematol Oncol 2013;6:32.
18. Pleyer L, Burgstaller S, Girschikofsky M, Linkesch W, Stauder R, Pfeilstocker M, *et al*. Azacitidine in 302 patients with WHO-defined acute myeloid leukemia: Results from the Austrian Azacitidine Registry of the AGMT-Study Group. Ann Hematol 2014;93:1825-38.
19. Thépot S, Itzykson R, Seegers V, Recher C, Raffoux E, Quesnel B, *et al*. Azacitidine in untreated acute myeloid leukemia: A report on 149 patients: Azacitidine in frontline AML. Am J Hematol 2014;89:410-6.
20. Lübbert M, Rüter BH, Claus R, Schmoor C, Schmid M, Germing U, *et al*. A multicenter phase II trial of decitabine as first-line treatment for older patients with acute myeloid leukemia judged unfit for induction chemotherapy. Haematologica 2012;97:393-401.
21. 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;30:2670-7.
22. Kadia TM, Thomas XG, Dmoszynska A, Wierzbowska A, Minden M, Arthur C, *et al*. Decitabine improves outcomes in older patients with acute myeloid leukemia and higher blast counts. Am J Hematol 2015;90:E139-41.
23. Kantarjian H, Ravandi F, O'Brien S, Cortes J, Faderl S, Garcia-Manero G, *et al*. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. Blood 2010;116:4422-9.
24. Raffoux E, Cras A, Recher C, Boëlle PY, de Labarthe A,

Turlure P, *et al*. Phase 2 clinical trial of 5-azacitidine, valproic acid, and all-trans retinoic acid in patients with high-risk acute myeloid leukemia or myelodysplastic syndrome. Oncotarget 2010;1:34-42.

25. Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner 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;115:453-74.
26. Cashen AF, Schiller GJ, O'Donnell MR, DiPersio JF. Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. J Clin Oncol 2010;28:556-61.
27. 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 and 30% blasts. Blood 2015;126:291-9.