DNA Hypomethylating Agents as Maintenance Therapy for Acute Myeloid Leukemia in Elderly Patients: a Systematic Review

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ABSTRACT

Background: AML is an aggressive haematological malignancy. Although advanced strategies we have reached for acute myeloid leukemia treatment to achieve complete remission, relapse is still common and overall survival is very poor specially in elderly patients. That leads to the need for using maintenance therapy that can help in delaying relapse and prolonging survival rate. DNA hypomethylating agents azaictidine and decitabine have been used and had a good promising result on this group of patients but no direct clinical trials performed to compare the two agents. In this systematic review we reviewed the literature for comparison between hypomethylating agents as maintenance therapy in elderly AML patients.

Aim of the Work: Perform a systematic review to assess the efficacy and safety of different hypomethylating agents (Azacitidine and Decitabine) as maintenance therapy for acute myeloid leukemia in elderly patients.

Methodology: In this systematic review, we searched Medline via PubMed, Web of Science, and CENTRAL from their inception till April 2021. A total of 296 records were obtained. After screening, 9 randomized controlled trials including 1046 patients were included.

Results: Our results showed that, treating patients with azacitidine or decitabine as maintenance therapy provided improved outcomes in terms of overall survival, disease free survival, relapse compared to placebo or supportive care. Direct comparison showed that azacitidne was superior to decitabine in terms of relapse and remission. However, there was no significant results in other outcomes.

Conclusion: Compared to standard supportive care or placebo, azacitidine or decitabine as maintenance therapy yields both better outcomes, including overall survival, disease free survival, relapse and remission. However, azacitidne was superior to deciatabine in delaying relapse. Although, indirect head-to-head comparisons, low certainty of evidence was found when comparing azacytidine and decitabine for other outcomes. The superiority of either agent cannot be confirmed in this study except in relapse rate and head-to-head clinical trials are still required to provide more information about the efficacy and safety of the two agents.

Keywords: Acute Myeloid Leukemia; DNA Hypomethylating agents; Azacitidine; Decitabine; Maintenance therapy

INTRODUCTION

Acute myeloid leukemia (AML) is an aggressive, genetically heterogeneous disease characterized by clonal proliferation and loss of differentiation of myeloid stem cells in the bone marrow resulting in impaired hematopoiesis ***(Kouchkovsky and Abdul-Hay, 2016)***.

AML accounts for 80% of all acute leukemia in adults, presented by diverse outcomes with poor prognosis and high mortality rate ***(Vakiti and Mewawalla, 2020).*** Elderly patients represent the majority of AML cases with a median age of 67 years at diagnosis ***(Siegel et al., 2018)***.

Over the last decades, many studies have been done to reveal the mystery of the pathogenesis and molecular changes in this complex disease. It was discovered that AML is not caused by a single causative agent alone but by an interplay between genetic, epigenetic and molecular abnormalities such as chromosomal abnormalities, genetic mutations or both. Genetic mutations alone account for more than 97% of the cases ***(Prada-Arismendy et al., 2017)***.

Recently, several targeted therapies were introduced in combination with standard chemotherapy and have achieved major progress in the treatment strategies with an obvious improvement in the complete remission (CR) rate in AML patients ***(Winer and Stone, 2019)***. However, the rate of relapse remains the toughest obstacle to prolong survival in these patients and represents a difficult challenge against the treatment either in the post-consolidation or posttransplantation ***(Bose et al., 2017)***.

Maintenance therapy could be the key to solve this problem, that's why many studies have been conducted to prolong overall survival and improve outcomes especially among the elderly or high-risk AML patients unfit for intensive therapy ***(McMahon and Luger, 2019)***. Therefore, several recent studies or strategies have been evaluated as maintenance therapy includes immunotherapy (interferon, interleukin-2 (IL- 2), anti CD33 monoclonal antibody and checkpoint inhibitors), molecularly targeted agents (FLT-3, IDH, and Bcl-2 inhibitors), and epigenetic hypomethylating agents (HMAs): 5-azacitidine and Decitabine ***(Molica et al., 2019)***.

Epigenetic modifiers as HMAs are pyrimidine nucleoside analogs of cytidine which incorporate with DNA during replication, making irreversible covalent bonds with DNA methyltransferase enzyme (DNMT). This leads to depletion of the intracellular level of DNMT, a reversal of DNA hypermethylation on silenced tumor suppressor genes, and reactivation of these genes, and induction of apoptosis ***(Hackanson and Daskalakis, 2014)***.

Different HMAs such as azacitidine and decitabine are approved by Food and Drug Administration (FDA) for AML treatment and are used as a maintenance safe therapy with more promising responses than supportive care alone ***(Schroeder et al., 2018)***.

However, the comparison between different HMAs (Azacitdine and Decitabine) has not been conducted directly in maintenance therapy in AML elderly patients and there is still a problem to choose between them. It depends totally on the experience of the treating physician.

AIM OF THE WORK

We aim to perform a systematic review to assess the efficacy and safety of different hypomethylating agents (Azacitidine and Decitabine) as maintenance therapy for acute myeloid leukemia in elderly patients.

PATIENTS AND METHODS

This systematic review was conducted by following the Cochrane guidelines for the conduction of systematic reviews and meta-analyses and the guidelines of Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statements ***(Moher et al., 2009).***

Search Eligibility Criteria: ***We included the studies with the following criteria:***

Population: Elderly patients with acute myeloid leukemia, **Intervention:** HMAs, such as azacitidine or decitabine, as maintenance therapy (alone or combined with other therapeutic agents), **Comparison:** Studies comparing HMAs, as maintenance therapy after standard therapy/remission versus Placebo or standard supportive care, **Outcome:** Overall survival, disease frees survival (DFS) Relapse Adverse effects and **Study design:** Randomized controlled trials (RCTs).

We excluded all the following: Case reports, Case series, Animal studies and Studies in other languages than English.

Search Strategy for Identification of Studies: We performed a comprehensive electronic search through the following databases: Medline via PubMed, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), The used keywords in the research are: Acute myeloid leukemia OR AML, hypomethylating agents, azacitidine, decitabine, maintenance therapy, elderly patients‖ and adults and The search was done with no limit regarding the year of publication.

Screening: Retrieved citations were imported into EndNote for duplicates removal, chosen citations were imported into Rayyan for systematic review software, Two reviewers screened all titles and abstracts of trials independently based on the eligibility criteria followed by a full texts screening and their relevant references.

Data Extraction: All extracted data were tabulated in a predefined Microsoft Excel spreadsheet.

The extracted data were included the following: Characteristics of the included studies and intervention, Baseline characteristics of studied participants, Study outcomes.

Quality Assessment: We evaluated the methodological quality of included studies using the Cochrane risk of bias assessment tool, clearly described in (chapter 8.5) of the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 ***(Higgins et al., 2019)*****,** to assess the risk of bias within included RCTs.

Statistical Analysis:

Data Synthesis: Statistical analysis was performed using Review Manager (version 5.4). Continuous outcomes were pooled as mean difference (MD) or standardized mean difference (SMD) using inverse variance method, and dichotomous outcomes will be pooled as odds ratio (OR) using Mantel-Haenszel method. The random-effects method was used under the assumption of existing significant clinical and methodological heterogeneity.

Assessment of Heterogeneity: We assessed heterogeneity by visual inspection of the forest plots, chi-square, and I-square tests. Chi-square p-value less than 0.1 denote significant heterogeneity while I^2 values show no important heterogeneity between 0% and 40%, moderate heterogeneity from 30% to 60%, substantial heterogeneity from 50% to 100%. So we used 50 % as a cut of point for heterogeneity. In case of I^2 value below 50%, we used fixed effect model while in I^2 value above 50%, we used random effect model.

RESULTS

In the present study, we searched Medline via PubMed, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) from their inception till April 2021. A total of 296 records were obtained. After removing duplicates, 251 unique records were screened by title and abstract. A total of 206 trials were excluded due to ineligibility and 45 potentially eligible records were included for full-texts screening. Finally, 9 studies were included in the present systematic review and meta-analysis Figure 1.

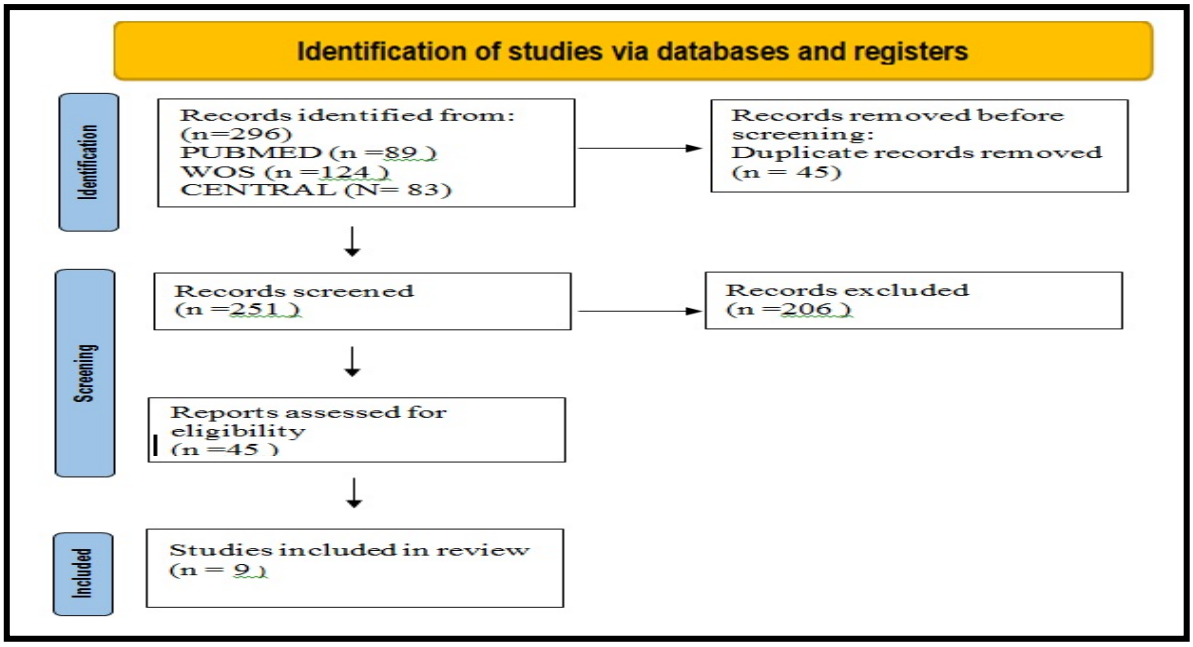

Figure (1): Steps of studies search, screening and selection

Characteristics of the Included Studies:

Table (1): Baseline characteristics of included studies

Study ID	Hypomethylation Agent	N		Age		Male / Female		Follow up
		Hypomethylation agent	Control	Hypomethylation agent	Control	Hypomethylation agent	Control	
Huls et al 2019	Azacitidine	56	60	69	69	35/21	33 / 27	41.4 months
Wei et al 2019	Azacitidine	238	234	68	68	118/120	127/107	41.2 months,
Boumber et al 2011	Decitabine	20	25	62	53	(19 male and 26 female)		44.9 months
Oliva et al 2018	Azacitidine	27	27	67	70.4	17/10	14/13	
Cuzzola et al 2016	Azacitidine	18	13	67.8	71.5	10\8	4\9	
Oliva et al 2019	Azacitidine	27	27	69				9.9 months
Huls et al 2017	Azacitidine	52						
Foran et al 2019	Decitabine	61	59	69				49.8 months
Ritchie et al 2013	Decitabine	102		66		52/48		

Table (2): Baseline characteristics of included studies (Continue).

Study ID	Hypomethylation agent	Cytogenetics		ECOG	
		Hypomethylation agent	Control	Hypomethylation agent	Control
Huls et al 2019	Azacitidine	Unfavorable (23%)	Unfavorable (16%)		
Wei et al 2019	Azacitidine	Poor (15%) Intermediate (85%)	Poor (13%) Intermediate (87%)	0 (49%) 1 (42%) 2 or 3 (9%)	0 (47%) 1 (45%) 2 or 3 (7%)
Boumber et al 2011	Decitabine	Intermediate (75%) Unfavorable (25%) Favorable (0%)	Intermediate (76%) Unfavorable(20) Favorable (4%)		
Oliva et al 2018	Azacitidine	Good (4%) Intermediate (70%) Poor (15%) Unfavorable 11%)	Good (0%) Intermediate (81%) Poor (15%) Unfavorable 4%)		
Cuzzola et al 2016	Azacitidine	Good (6%) intermediate (72% Poor (11%) Unknown (11%)	Good (0%) Intermediate (77%) Poor (23%) Unknown (0%)		
Oliva et al 2019	Azacitidine				
Huls et al 2017	Azacitidine				
Foran et al 2019	Decitabine	Intermediate (74.2%)		0 or 1 (96%).	
Ritchie et al 2013	Decitabine	Adverse (30%) Intermediate (70%)		0 (24.5%), 1 (49.0%), 2 (18.6%), 3(6.9%) one was unknown	

Relapse and Remission:

Table (3): Relapse and complete remission rate

Study ID	Hypomethylation Agent	Relapse rate n \ total		Complete remission n \ total	
		Hypomethylation agent	Control	Hypomethylation agent	Control
Huls et al 2019	Azacitidine	13\56	27\60		
Boumber et al 2011	Decitabine	10\20	15\25	10\20	
Oliva et al 2018	Azacitidine	17\127	19\27		
Cuzzola et al 2016	Azacitidine	11\18	10\13		
Oliva et al 2019	Azacitidine	18\27	21\27		
Ritchie et al 2013	Decitabine			16\102	

Azacitidine significantly decreased relapse rates (OR=0.48, 95% CI = [0.28, 0.83], I^2 =0%, p value =0.81) While Decitabine did not significantly decreased the relapse rate (OR=0.67, 95%CI = [0.20, 2.18]) Figure 2.

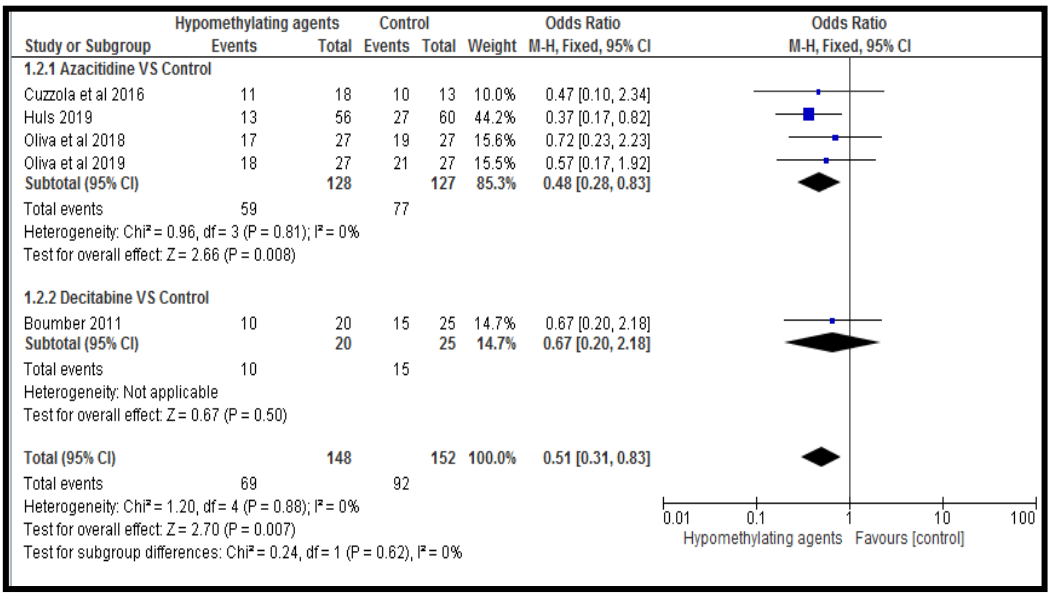

Figure (2): Forst plot for relapse rates across studies

Overall Survival:

Table (4): Survival rates across the studies.

Study ID	Agents	OS		1-year-OS		2-year -OS		3-year-OS	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Huls et al 2019	Azacitidine			84%.	70% (NS)				
Wei et al 2019		24.7 months	14.8 months (S)	72.80%	55.80%	50.60%	37.10%		
Huls et al 2017		(NS)							
Oliva et al 2018		Ten in each arm died (NS)							
Ritchie et al 2013	Decitabine	14.75 months							
Boumber et al 2011		45%	36% (NS)						
Foran et al 2019		82 deaths (46 CON, 36 DAC). (NS)							

(S): statistically significant difference, (NS): No statistically significant difference, CON: control, DAC decitabine, OS: overall survival

Disease Free Survival

Table (5): Disease free survival rates across the studies

Study ID	Agents	DFS		DFS at 6 months		DFS at 1 year		DFS at 3 years	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Huls et al 2019	Azacitidine					44%	20%	32%	16%
Wei et al 2019		10.2 months	4.8 months	67.40%	45.20%				
Oliva et al 2018		11 months	5 months						
Oliva et al 2019		11 months	9 months						
Huls et al 2017						63%	39%		
Foran et al 2019	Decitabine	90 DFS events (47 CON, 43 DAC),							
Boumber et al 2011		35%	32%						

CON: control, DAC Decitabine, DFS: disease fee survival

Table (6): Adverse events.

Study ID	Agents	Toxicity	Event n (%)	Total
Wei et al 2019	Azacitidine	Thrombocytopenia	79 (33%)	236
Boumber et al 2011	**Decitabine**		14 (70%)	20
Wei et al 2019	Azacitidine	Neutropenia	105 (44%)	236
Boumber et al 2011	**Decitabine**		19 (95%)	20
Oliva et al 2018	Azacitidine		9 (33%)	27
Wei et al 2019	Azacitidine	Weakness/fatigue	70 (30%)	236
Wei et al 2019	Azacitidine	Constipation	91 (39%)	236
Wei et al 2019	Azacitidine	Nausea	153 (65%)	236
Wei et al 2019	Azacitidine	Dizziness	25 (11%)	236
Wei et al 2019	Azacitidine	Anemia	48 (20%)	236
Wei et al 2019	Azacitidine	Diarrhea	119 (50%)	236

DISCUSSION

In our systematic review and meta-analysis, 9 Randomized controlled trials including 1046 patients were included. The average age of the patients within the included studies ranged from 55-67 years old and there was a slight male predominance. Treating patients with azacitidine or decitabine as maintenance therapy provided improved outcomes in terms of overall survival, disease free survival, relapse compared to placebo or supportive care. Indirect head-to-head comparison, showed that azacitidne was superior to deciatabine in terms of relapse and remission.

Our result showed that Azacitidine significantly decreased relapse rates (OR=0.48, 95% CI = [0.28, 0.83], I^2=0%, p value =0.81). While Decitabine did not significantly decreased the relapse rate (OR=0.67, 95%CI = [0.20, 2.18]).

In concordance with our findings, ***Huls et al. (2019)***, showed that azacitidine delays relapse in patients in complete remission after 2 cycles of intensive chemotherapy. Also ***Oliva et al. (2019),*** showed that 18 patients receiving azacytidine relapsed compared to 21 patients recieved the supportive care only.

In addition, ***Oliva et al. (2018),*** relapse rate was 63% with patients received azacitidine compared to 70% in the patients received supportive care only (ref.) showed that 60 % patients reciving azacitidne had relapsed compared to 77 % patinets with supportive care. All these results were statistically significant.

However Boumber et al, concerned with decitabine and showed that no statistically significant results according to relapse rate with this drug.

These data may support the use of azacitidine in clinical management of older patients as a maintence therapy is better than decitabine to delay relapse.

Patients treated with Azacitidine had a significant increase in survival duration compared to the control group (24.7 vs. 14.8 months) ***(Wei et al., 2019)***. While in ***Huls et al., (2017); Oliva et al. (2018),*** there was no significant difference in survival rates between azacitidine and control arms.

None of the patients treated with Decitabine showed increase in survival rate compared to the control group ***(Boumber et al., 2012; Foran et al., 2019)***. Additionally, the patients had a lower survival duration than patients treated with Azacitidine 14.75 months in ***Ritchie et al. (2013)*** VS 24.7 months in ***Wei et al. (2019)***.

Concerning to disease free survival, ***Huls et al. (2017); Oliva et al. (2018); Wei et al. (2019),*** showed that azacitidine significantly increased disease free survival durations compared to the control. Although, in ***Oliva et al. (2019)*** there was a modest increase in survival duration.

However, disease fee survival at one year was higher in ***Huls et al. (2017)*** than ***(Huls et al., 2019)***. On the other hand Decitabine did not affect disease free survival duration ***(Boumber et al., 2012; Foran et al., 2019)***.

Concerning to adverse effects, Only two studies reported adverse events for Azacitidine ***(Oliva et al., 2018; Wei et al., 2019),*** and only (Boumber et al., 2012) reported adverse events for Decitabine. The advserse events for Azacitidine was as following, 33% Thrombocytopenia, 44% and 33% Neutropenia, 30% fatigue, 39% Constipation, 65% Nausea, 11 % Dizziness, 20% Anemia, and 50% Diarrhea Pooled estimated for Neutropenia was (OR=42.1%, 95% CI = [33.8%, 50.4%], I2 =20.32%, p value =0.263). The rate of adverse events was higher in Decitabine arm: 70% Thrombocytopenia, and 95% Neutropenia.

CONCLUSION

Compared to standard supportive care or placebo, azacitidine or decitabine as maintenance therapy yields both better outcomes, including overall survival, disease free survival, relapse and remission. However, azacitidne was superior to deciatabine in delaying relapse. Although, indirect head-to-head comparisons, low certainty of evidence was found when comparing azacytidine and decitabine for other outcomes. The superiority of either agent cannot be confirmed in this study except in relapse rate and head-to-head clinical trials are still required to provide more information about the efficacy and safety of the two agents.

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