European Review for Medical and Pharmacological Sciences 2021; 25: 2577-2590

Hypomethylating agents for elderly patients with acute myeloid leukemia: a PRISMA systematic review and meta-analysis

R.-J. ZHANG, J.-H. ZHAI, Z.-J. ZHANG, L.-H. YANG, M.-F. WANG, C.-X. DONG

Department of Hematology, The Second Hospital of Shanxi Medical University, Taiyuan, China

Abstract. – OBJECTIVE: Abnormal DNA methylation plays a critical role in acute myeloid leukemia (AML) pathogenesis and hypomethylating agents (HMAs) such as decitabine (5-aza-29-deoxycytidine) and azacitidine (5-azacytidine) are considered efficacious for treating AML. This study aimed to identify if HMAs have therapeutic advantages compared with conventional care regimens (CCR) or placebo in elderly AML patients.

MATERIALS AND METHODS: We systematically searched PubMed, Embase, and Cochrane Central Register of Controlled Trials from inception to November July 15, 2020. Randomized controlled trials that compared the efficacy and adverse events associated with HMAs, CCR, or placebo were searched. RevMan 5.3 software was used to calculate the hazard ratio (HR) and risk ratio (RR) with a 95% confidence interval (CI).

RESULTS: Seven trials with a total of 1966 participants were included. Meta-analyses showed that the overall survival of HMAs was better than that of CCR [HR=0.76, 95% CI (0.69-0.85), (p<0.01)], and the complete remission rate of elderly AML patients was increased by HMAs compared with CCR [RR=1.46, 95%CI (1.08-1.99), p=0.01)]. HMA treatment showed higher incidence of neutropenia [RR=1.30 (95%CI 1.07-1.59, p=0.008)], thrombocytopenia [RR=1.14 (95%CI 1.01-1.59, p=0.04)], and pneumonia [RR=1.37 (95%CI 1.06-1.76, p=0.02)] compared with CCR.

CONCLUSIONS: Although HMAs cause a higher incidence of adverse events such as neutropenia, thrombocytopenia, and pneumonia, demethylation drugs are well-tolerated and effective for treating AML in the elderly.

Key Words:
Acute myeloid leukemia, DNA hypomethylating agents, Elderly patients, Systematic review, Meta-analysis.

Abbreviations

CI: Confidence interval; RCT: Randomized controlled trials; RR: Risk ratios; HR: Hazard ratio; AZA: Azacitidine; DAC: Decitabine; OR: Overall survival; CR: Complete response; CCR: Conventional care regimens; IC: Intensive chemotherapy; LDAC: Low-dose cytarabine; BSC: best supportive care; AML: Acute myeloid leukemia; HMAs: hypomethylating agents; MDS: myelodysplastic syndromes.

Introduction

Acute myeloid leukemia (AML) is an aggressive stem cell malignancy characterized by the clonal expansion of abnormal hematopoietic progenitors in the bone marrow[1]. It is mostly seen in elderly individuals, with a median age at diagnosis of 68 years; the age-specific incidence rates are below 10/100,000 among individuals <65 years, while they progressively increase to 28.5/100,000 for individuals aged 80-84 years[2]. Although therapeutic regimens like "3 + 7" chemotherapy, hematopoietic stem cell transplantation, and supportive care show significant effect among patients younger than 60 years[3], 70%-80% achieve complete remission[4], and 35%-40% are cured[5]. Nevertheless, because of resistance to conventional chemotherapy, adverse cytogenetics, and frequent comorbidities[6], the prognosis of elderly patients (aged >65 years) with AML still remains poor[7], with a median overall survival (OS) time of 9.2 months and a 5-year OS rate of 13.5%[8]. Moreover, primary refractory or resistant AML can hardly be cured by conventional salvage therapy, and therefore new therapeutic approaches are urgently needed for these patients[9,10].

Abnormal DNA methylation plays a crucial role in AML pathogenesis[11,12] and is known to regulate the expression of tumor suppressor genes and oncogenes, promoting dysplasia and blast transformation[13]. With the breakthrough in molecular biology research on the characteris-

Corresponding Author: Rui-Juan Zhang, MD; e-mail: 13593169668@163.com; zhangruijuan@sxmu.edu.cn

tics and pathogenesis of AML, hypomethylating agents (HMAs) such as decitabine (5-aza-29-deoxycytidine) and azacitidine (5-azacytidine) have become research hot spots in treating myelodysplastic syndromes (MDS) and AML. The National Comprehensive Cancer Network (NCCN) recommends HMAs as the preferred treatment option for elderly AML patients with unfavorable cytogenetics, poor molecular markers, a history of hematologic disorders, therapy-related AML, or unfit performance status[14]. Over the last few decades, HMAs have been widely used for the treatment of MDS[15,16], and studies have also shown that these drugs show certain effects as first-line and rescue treatment for AML[17,18]. Nevertheless, the survival outcome data with regard to HMAs in elderly AML patients have been inconsistent[19,20]. Therefore, this systematic review and meta-analysis aimed to evaluate the efficacy of HMAs and their adverse effects when treating older AML patients.

Materials and Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines **(Supplementary File 1: PRISMA 2015 Checklist)**[21].

Search Strategies

Relevant randomized controlled trials (RCTs) that were published electronically in the PubMed, Embase, and Cochrane Central Register of Controlled Trials (Central) databases were searched from inception to July 15, 2020, without any restrictions to language. The search terms were "acute myeloid leukemia", "azacitidine", "decitabine", "elderly patients", and "randomized controlled trial". A bibliography of identified articles and other documents from relevant references were manually searched to identify any additional relevant trials. Two study researchers designed and performed the search strategy **(Supplementary File 2: Search strategies)**.

Eligibility Criteria

The eligibility criteria were (1) Phase II and III RCTs, (2) with adult patients aged ≥55 years, (3) with morphologically proven diagnosis of AML and with no previous allogeneic stem cell transplantation, (4) treated with HMAs (such as azacitidine, decitabine or guadecitabine) and compared with those of conventional care regimens (CCR) including best supportive care (BSC), low-dose cytarabine or intensive chemotherapy in a setting of first-line treatment, and (5) studies that evaluated complete response (CR) rate or overall survival (OR). The trial data from the most recent publication were used only once in the analysis.

Exclusion Criteria

Trials were excluded if any of the following factors were identified: (1) conference abstracts, case reports, editorials, review articles, and cell or animal studies, (2) studies with insufficient information concerning OR or CR, (3) patients diagnosed with myelodysplastic syndrome (MDS), (4) the age of the participants is not limited, and (5) retrospective studies.

Study Selection

Two reviewers (AA and ZZ) independently screened the titles and abstracts of all trials and included the trials based on the eligibility criteria. The full-text articles and their relevant references were selected for further assessment. Any disagreements were settled by discussion between the two reviewers, and a third independent reviewer (BB) was invited to participate if necessary.

Data Extraction

Two reviewers (AA and ZZ) independently read and extracted the data using a standardized form. The following data were extracted from each study: population size, median age, bone marrow (BM) blast count, cytogenetic risk categories, treatment and dosing regimens, median treatment duration, and adverse events (AEs) of interest. The co-primary endpoints such as OS, CR, neutropenia, leukopenia, thrombocytopenia, anemia, and febrile neutropenia were included. All data were recorded in Excel 2016 (Microsoft, Redmond, WA, USA).

Assessment of Bias Risk

The Cochrane Collaboration's tool[22] was used to evaluate the random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. The risk of bias was rated as high, unclear, or low. Two reviewers (WW and YY) independently evaluated the risk of bias in each study, and any disagreements were settled down by discussion with a third independent reviewer (BB).

Statistical Analysis

Data analyses were carried out using Review Manager (Version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, London, UK). A 95% confidence interval (CI) with risk ratio (RR) or hazard ratio (HR) was used to present the results of the meta-analysis. The Cochrane Q statistic was used to estimate the heterogeneity, and the I^2 test was used to quantify the inconsistency[23]. $p>0.10$ and $I^2<50\%$ indicated an acceptable level of heterogeneity, and a fixed-effects model was adopted; otherwise, a random-effects model was adopted. Publication bias was evaluated using a funnel plot for analyses with ≥10 studies. If no publication bias was observed, then a symmetrical scatter forming a triangular "funnel" could be seen. If publication bias exists, then this might suggest missing negative studies and results in an unbalanced shape. Sensitivity analysis was conducted by deleting one study at a time to assess the stability of the results. A two-tailed p-value of <0.05 was considered statistically significant in all statistical tests.

Results

Literature Search Results

The literature search yielded 163 potential abstracts, and 105 studies were removed because of duplications. After reviewing the titles and abstracts, 21 studies were reviewed (full-text) for eligibility. Of these, 14 studies were excluded due to duplications, post hoc or without primary endpoints of interest, and the remaining six articles and one abstract [19,20,24-28] were included in this meta-analysis (Figure 1), which included two Phase II trials (n=292)[20,26] and five Phase III trials (n=1674)[19,20,24,25,37] published between 2010 and 2019. The characteristics of these trials are summarized in Table I.

Publication Characteristics

All trials included patients with morphologically confirmed AML and aged 55 years or more. A total of 1966 patients were included in this analysis. Of these, 976 were treated with either azacitidine (n = 719)[19,24-27] or decitabine (n = 257)[20,28], and the remaining 990 were treated with CCR includ-

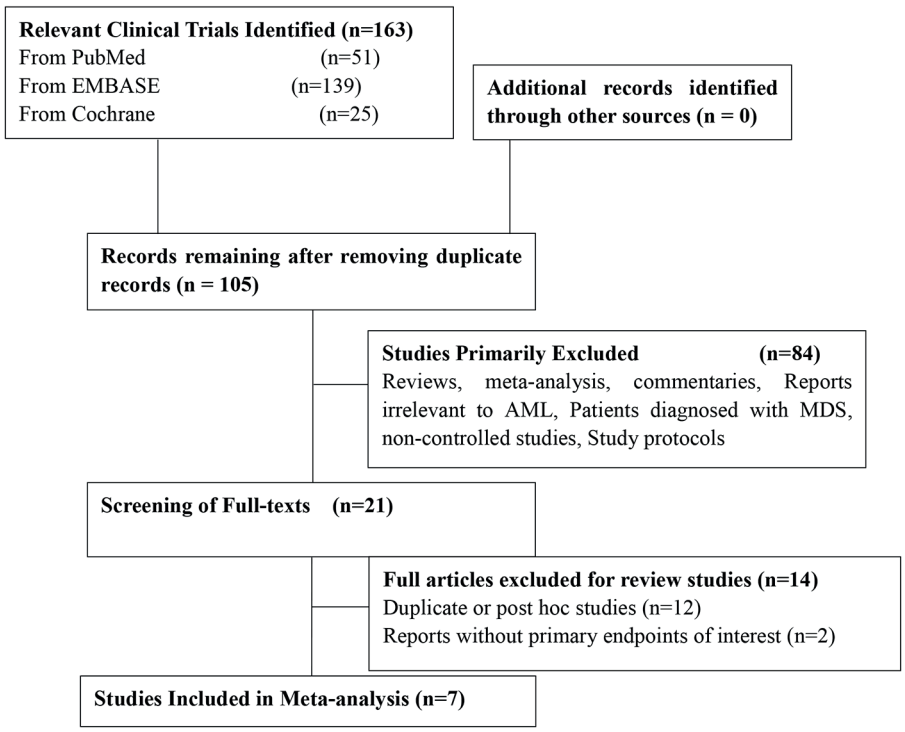

Figure 1. Flowchart presenting the steps of literature search and selection.

Table I. Characteristics of Included Trials.

Reference	HMA	Country	Sample size (M/F)		Median age, years		Cytogenetic risk group, n (%)	BM Blast	Median F/U, months
			Intervention	Comparison	Intervention	Comparison			
Fenaux et al[19] 2010	AZA	France, UK, Sweden, Italy, Spain, USA, Germany, Australia	37/18	41/17	70	70	Intermediate: 81 (71.7) Normal: 52 (46.0) Poor risk: 27 (23.9) Missing: 5 (4.4)	**Intervention:** 23.0 (20.0-34.0) % **Comparison:** 23.1(13.0-68.9) %	20.1
Dombret et al[24] 2015	AZA	France, Poland, USA, Belgium, Korea, UK, Canada, Italy, Spain, Germany, Australia	139/102	149/98	75	75	Intermediate: 306 (63.1) Poor risk: 174 (35.8)	**Intervention:** 70.0 (2.0-100.0)% **Comparison:** 72.0 (2.0-100.0)%	24.4
Huls et al[25] 2019	AZA	Netherlands, Belgium	35/21	33/27	69	69	Unfavorable risk: 23 (19.8) intermediate: 93 (80.2)	NR	41.4
Seymour et al[26] 2017	AZA	France, Poland, USA, Belgium, Korea, UK, Canada, Italy, Spain, Germany, Australia	81/48	78/55	76	75	Intermediate: 124 (47.3) Poor risk: 138 (52.7)	**Intervention:** 65.0 (27-99)% **Comparison:** 70.0 (26-100)%	NR
Wei et al[27] 2019*	AZA	International	238	234	68		NR	NR	41.2
Kantarjian et al[28] 2012	DAC	International	137/105	151/92	73	73	Intermediate: 306 (63.4) Poor risk: 174 (36.0)	20-30%: 123 (25.2%) 30-50%: 141 (29.3%) >50%: 206 (42.7%)	NR
Jacob et al[20] 2015	DAC	India	12/3	12/3	65	62	Unsatisfactory 15 (50) Normal karyotype 10 (33.3) Inv(16) 1 (3.3) Abnormality of chromosome 8 2 (6.7) Abnormality of chromosome 7 1 (3.3)	20-30%: 10 (33.3%) 30-50%: 12 (40%) >50%: 8 (26.7%)	NR

NR = not reported, AZA = Azacitidine, DAC = Decitabine, HMA = hypomethylating agents, BM = bone marrow. *Abstract.

Table continued

Table I. (*Continued*). Characteristics of Included Trials.

Reference	Treatment regimens	Median treatment duration	OS, months	Adverse event, n(%)
Fenaux et al[19] 2010	**Intervention:** Azacitidine (subcutaneously 75 mg/m^2/ day for 7 days Q28 days for at least 6 cycles) **Comparison:** CCR (BSC, LDAC 20 mg/m^2/day for 14 days Q28 days for at least 6 cycles, IC)	**Intervention:** 34 (15-79) days **Comparison:** LDAC, 35 (15-77) days, IC, 2.5 (1-3c) cycles, BSC,6 (2-19) months.	**Intervention:** 24.5 (14.6-NR) **Comparison:** 16 (11.5-17.5)	**Intervention:** Anemia: 30 (56.6), Neutropenia: 50 (94.3), Thrombocytopenia: 48 (90.6) **Comparison:** Anemia: 36 (67.9), Neutropenia: 44 (83.0), Thrombocytopenia: 44 (83.0)
Dombret et al[24] 2015	**Intervention:** Azacitidine (subcutaneously 75 mg/m^2/ day for 7 days Q28 days for at least 6 cycles **Comparison:** CCR (BSC, LDAC 20 mg/m^2/day for 14 days Q28 days for at least 6 cycles, IC)	**Intervention:** 6 (1-28) cycles, **Comparison:** LDAC, 4 (1-25) cycles, IC, 2 (1-3) cycles, BSC, 65 (6-535) days.	**Intervention:** 10.4 (8.0-12.7) **Comparison:** 6.5 (5.0-8.6)	**Intervention:** Anemia: 37 (15.7), Neutropenia: 62 (26.3), Thrombocytopenia: 56 (23.7), Febrile neutropenia: 66 (28.0), Pneumonia: 45 (19.1),Leukopenia: 16 (6.8), Hypokalemia: 12 (5.1) **Comparison:** Anemia: 43 (18.3), Neutropenia: 54 (22.9), Thrombocytopenia: 53 (22.5), Febrile neutropenia: 70 (29.8), Pneumonia: 33 (14.0), Leukopenia: 19 (8.1), Hypokalemia: 18 (7.7)
Huls et al[25] 2019	**Intervention:** Azacitidine (50 mg/m^2 sc for 5 days every 4 weeks for 12 cycles) **Comparison**: Observation (no further treatment)	**Intervention:** 1-4 cycles: 55 5-8 cycles: 44; 9-12 cycles: 37 **Comparison:** 1-4 months: 60 5-8 months: 39; 9-12 months: 28	NR	**Intervention:** 0 SAE, 42 (75), 1 SAE, 11 (20), 2 SAE, 2 (3), 3 SAE, 1 (2) **Comparison:** 0 SAE, 56 (93), 1 SAE, 4 (7)
Seymour et al[26] 2017	**Intervention:** Azacitidine (subcutaneously 75 mg/m^2/ day for 7 days Q28 days for at least 6 cycles **Comparison:** CCR (BSC, LDAC 20 mg/m^2/day for 14 days Q28 days for at least 6 cycles, IC)	NR	**Intervention:** 8.9 (6.9, 12.9) **Comparison:** 4.9 (3.8, 6.5)	**Intervention:** Anemia: 19 (15), Neutropenia: 28 (22), Thrombocytopenia: 33 (26), Febrile neutropenia: 29 (23), Pneumonia: 24 (19), Leukopenia: 8 (6), Hypokalemia: 9 (7) **Comparison:** Anemia: 21 (16), Neutropenia: 25 (19), Thrombocytopenia: 27 (21), Febrile neutropenia: 43 (33), Pneumonia: 18 (14), Leukopenia: 10 (8), Hypokalemia: 10 (8)
Wei et al[27] 2019	**Intervention:** Azacitidine (CC-486 300 mg QD for 14 days, Best supportive care 28-day cycles) **Comparison:** Placebo (QD for 14 days, Best supportive care 28-day cycles)	**Intervention:** 12 (1-80) cycles, **Comparison**: 6 (1-73) cycles.	**Intervention:** 24.7 **Comparison:** 14.8	**Intervention:** Nausea 152(64), Vomiting 140(59), Diarrhea 117(49), Neutropenia 98(41), Thrombocytopenia 55(23), Anemia 33(14), Infections 40(17) **Comparison:** Nausea 54(23), Vomiting 23(10), Diarrhea 49(21), Neutropenia 56(24), Thrombocytopenia 52(22) Anemia 30(13), Infections 19(8)
Kantarjian et al[28] 2012	**Intervention:** Decitabine (intravenously 20 mg/m^2 QD for 5 days, every 4 weeks) **Comparison:** TC (supportive care, or cytarabine 20 mg/m^2 QD for 10 days, every 4 weeks)	**Intervention:** 4 (1-29) cycles, **Comparison**: Cytarabine, 2 (1-30) cycles, SC, 2 (1-28) cycles.	**Intervention:** 7.7 (6.2-9.2) **Comparison:** 5.0 (4.3-6.3)	**Intervention:** Anemia: 15 (6), Neutropenia: 15 (6), Thrombocytopenia: 21 (9), Febrile neutropenia: 57 (24), Pneumonia: 48 (20), Leukopenia 47(20), Hypokalemia 27(11) **Comparison:** Anemia: 12 (5), Neutropenia: 7 (3), Thrombocytopenia: 11 (5), Febrile neutropenia: 33 (14), Pneumonia: 36 (15), Leukopenia 20(8), Hypokalemia 24(10)
Jacob et al[20] 2015	**Intervention:** Decitabine (intravenously 20 mg/m^2 QD for 5 days, every 4 weeks) **Comparison:** Low-dose cytarabine (subcutaneously 20 mg/m^2 QD for 10 days, every 4 weeks)	**Intervention:** 4 (1-7) cycles, **Comparison**: 4 (1-14) cycles.	**Intervention:** 5.5 (0.5-13) **Comparison:** 5.5 (0.5-17.1)	**Intervention:** Anemia: 8 (53.3), Neutropenia: 7 (46.7), Thrombocytopenia: 8 (53.3), Febrile neutropenia: 5 (33.3), Hypokalemia 2 (13.33), Mucositis 4 (26.67), Fatigue 4 (26.67), Hypocalcemia 3 (20.00) **Comparison:** Anemia: 7 (46.7), Neutropenia: 8 (53.3), Thrombocytopenia: 8 (53.3), Febrile neutropenia: 5 (33.3), Hypokalemia 2 (13.33), Mucositis 4 (26.67), Fatigue 5 (33.33), Hypocalcemia 2 (13.33)

NR = Not reported, OS = Overall survival, BSC = best supportive care, CCR = Conventional care regimens, IC=Intensive chemotherapy, LDAC = Low-dose cytarabine.

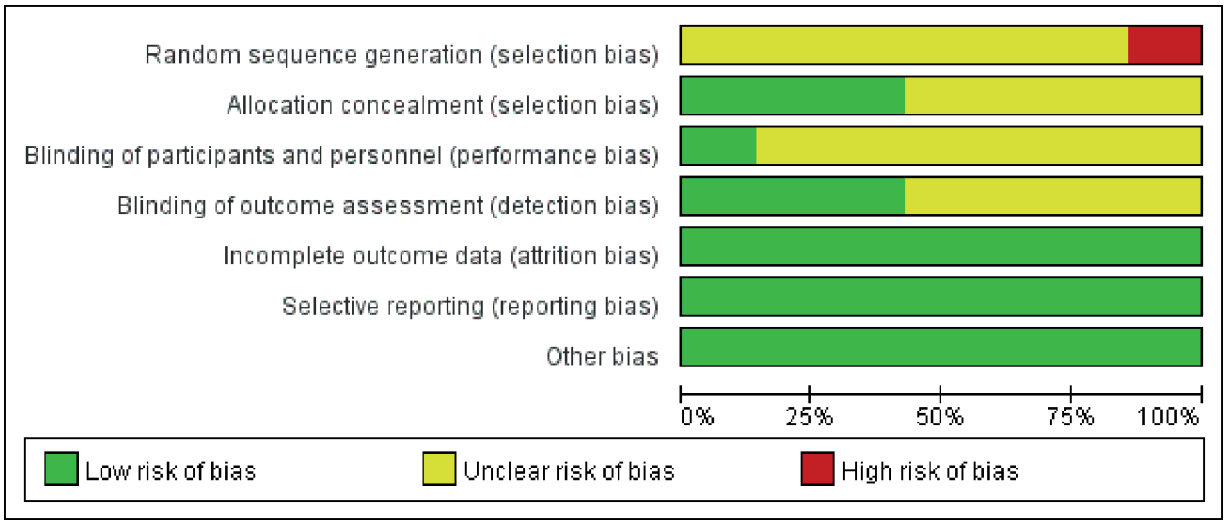

Figure 2. Risk of bias graph.

ing BSC, low-dose cytarabine (LDAC), intensive chemotherapy (IC), and placebo. The median age of patients on the selected trials ranged from 62 to 76 years. The median follow-up was reported in 4 studies[19,24,25,27]. Five studies were large, international, multicenter RCTs, with patients from the United States, United Kingdom, France, Italy, Australia, and other countries.

Risk of Bias

The bias analysis is shown in Figures 2 and 3. Six studies were open-labeled RCTs[19,20,24-26,28], and one study was a double-blinded RCT[27]. All trials reported randomization, one study did not perform adequate random sequence generation[20], and four studies did not perform adequate allocation[19,20,25,27]. The adequacy of blinding of participants and personnel (performance bias) was evaluated using blind methods for the researchers and participants in the study, and the adequacy of outcome assessment blinding was judged by a reviewer who was blind to the patient groups. One study performed blinding of participants[27]. In three studies, treatment response was assessed by a third-party specialist in related fields[24,26,28]. Randomization, follow-up, and safety analysis were well-designed and conducted. Thus, attrition bias and reporting bias were unlikely to exist.

HR of Overall Survival

All seven studies analyzed the OS between HMAs and control. The OS of the elderly AML patients who received AZA treatment showed significant prolongation compared to those who received traditional therapy [HR=0.73, 95% CI

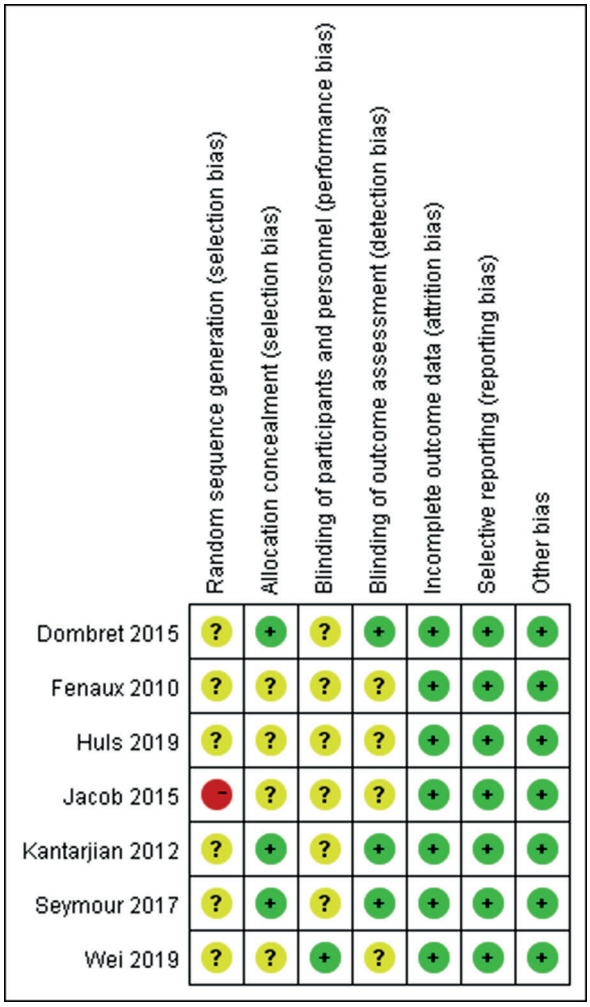

Figure 3. Risk of bias summary.

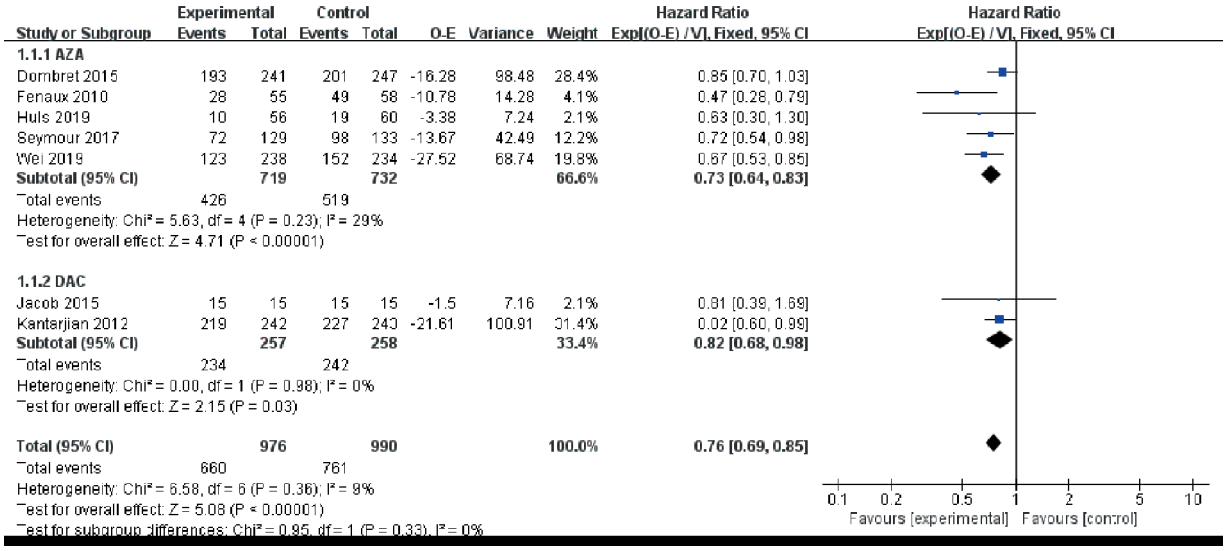

Figure 4. Forest plot of HR of OS with HMAs *vs.* CCR or Placebo. CCR=conventional care regimens, HMAs=hypomethylating agents, AZA=Azacitidine, DAC=Decitabine, HR=Hazard Ratio.

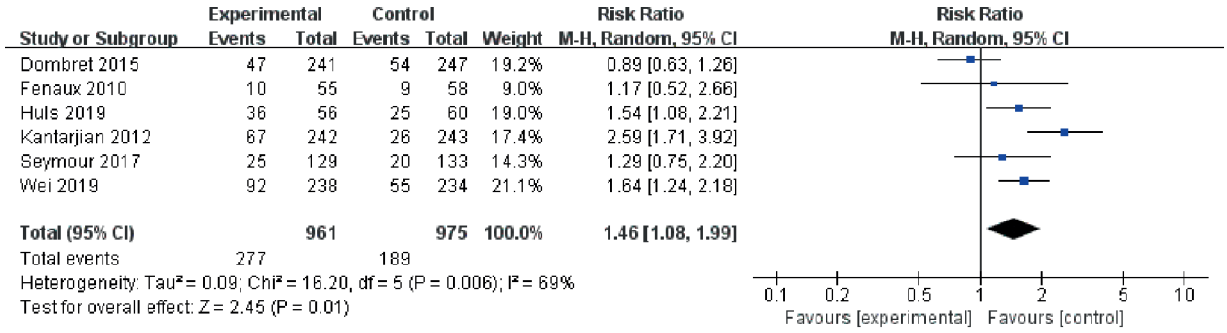

Figure 5. Forest plot of RR of CR with HMAs *vs.* CCR or Placebo. CCR=conventional care regimens, HMAs=hypomethylating agents, CR=complete remission, RR=risk ratio.

(0.64-0.83), (p<0.01)], while the group receiving DAC showed also showed significantly prolonged OS in elderly AML patients compared with the CCR group [HR=0.82, 95% CI (0.68-0.98), (p=0.03)] (Figure 4). There was no significant heterogeneity in the OS analyses across AZA studies (I^2=29%, p=0.23) and DAC studies (I^2=0%, p=0.98). The combined estimate demonstrated an association of HMA treatments with significantly better OS [HR=0.76, 95% CI (0.69-0.85), (p<0.01)], and there was no significant heterogeneity between the subgroups (I^2=0%, p=0.33).

RR of Complete Remission

Six studies[19,24-28] analyzed the CR rate, including five AZA studies and one DAC study. Compared with patients receiving CCR or placebo, the CR rate was significantly increased in elderly AML patients receiving HMA treatment [RR=1.46, 95%CI (1.08-1.99) (p=0.01)] (Figure 5). There was significant heterogeneity in the CR (I^2=69%, p=0.006) analyses among studies.

Adverse Events

All seven studies reported AEs, but one of them reported only the number of people with different AEs and lacked the number of specific AEs[25]. Thus, six studies were included for analyzing the AEs, in which the hematologic toxicity effects of HMAs for treating the elderly AML patients were compared.

RR of Neutropenia

For calculating the RR of neutropenia, six trials[19,20,24,26-28] with patients receiving HMAs *vs.*

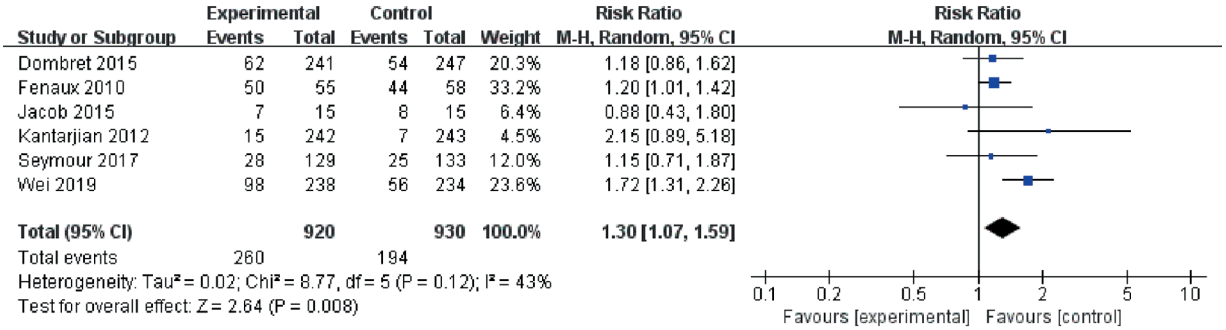

Figure 6. Forest plot of RR of neutropenia associated with HMAs *vs.* CCR or placebo.

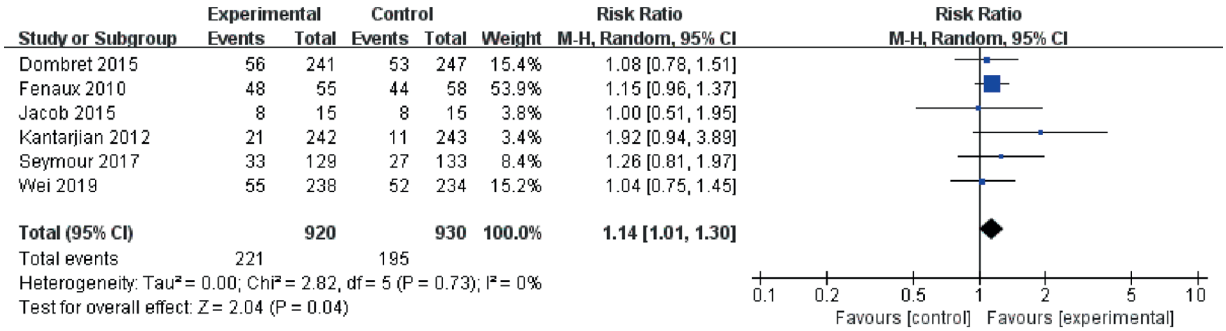

Figure 7. Forest plot of RR of thrombocytopenia associated with HMAs *vs.* CCR or placebo.

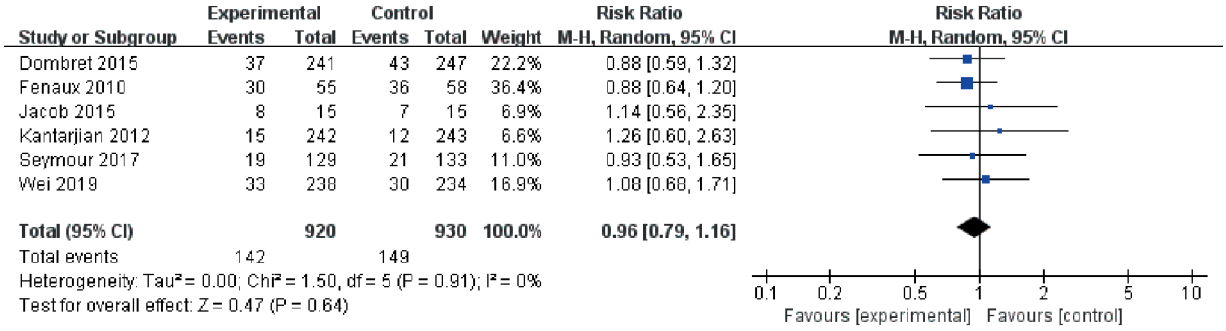

Figure 8. Forest plot of RR of anemia associated with HMAs *vs.* CCR or placebo.

CCR were analyzed (Figure 6). The pooled analysis showed that the administration of HMAs significantly increased the risk of neutropenia. The RR of neutropenia was 1.30 (95%CI 1.07-1.59, p=0.008). There was no significant heterogeneity in the RR of the neutropenia (I^2=43%, p=0.12) analysis among the studies.

RR of Thrombocytopenia

Thrombocytopenia was reported in six studies[19,20,24,26-28] (Figure 7). The pooled analysis showed that the administration of HMAs significantly increased the risk of developing thrombocytopenia. The RR of thrombocytopenia was 1.14 (95%CI 1.01-1.59, p=0.04), showing no significant heterogeneity (I^2=0%, p=0.73) among the studies.

RR of Anemia

For calculating the RR of anemia, six trials[19,20,24,26-28] with patients who received HMAs *vs.* CCR were used for analysis (Figure 8). Adminis-

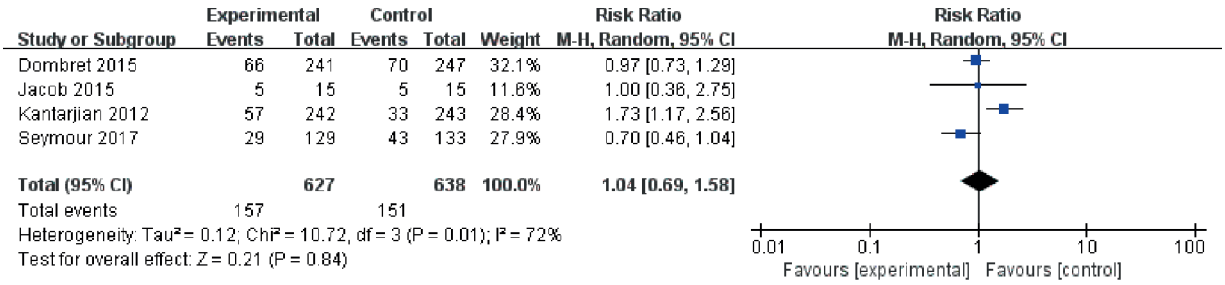

Figure 9. Forest plot of RR of febrile neutropenia associated with HMAs *vs.* CCR or placebo.

tration of HMAs showed no significant change in the risk of developing anemia. The RR of anemia was 0.96 (95%CI 0.79-1.16, p=0.64), showing no significant heterogeneity (I^2=0%, p=0.91) among the studies.

RR of Febrile Neutropenia

Febrile neutropenia was evaluated in four studies[20,24,26,28] (Figure 9). The pooled analysis showed that no HMAs increased the risk of developing febrile neutropenia. The RR of febrile neutropenia was 1.04 (95%CI 0.69-1.58, p=0.84), and substantial heterogeneity was observed (I^2=66%, p=0.01).

RR of Pneumonia

For pneumonia, three trials[24,26,28] with patients who received HMAs *vs.* CCR were used for analysis (Figure 10). The pooled analysis showed that the administration of HMAs significantly increased the risk of developing pneumonia. The RR of neutropenia was 1.37 (95%CI 1.06-1.76, p=0.02), and a low heterogeneity (I^2=0%, p=0.99) was observed among the studies.

RR of Leukopenia

For leukopenia, three trials[24,26,28] with patients who received HMAs *vs.* CCR were used for analysis (Figure 11). The results showed no significant differences in the risk of developing leukopenia between HMAs and CCR. The RR of leukopenia was 1.25 (95%CI 0.57-2.76, p=0.57), showing significant heterogeneity (I^2=77%, p=0.01) among the studies.

RR of Hypokalemia

For hypokalemia, four trials[20,24,26,28] with patients who received HMAs *vs.* CCR were used for analysis (Figure 12). The analysis results showed no significant differences in the risk of developing hypokalemia between HMAs and CCR. The RR of hypokalemia was 0.95 (95%CI 0.65-1.37, p=0.77), and no significant heterogeneity (I^2=0%, p=0.74) was observed among the studies.

Discussion

This systematic review and meta-analysis was intended to test whether HMAs have a better effect and milder AEs in elderly patients with AML. The combined analyses revealed statistically significant differences in OS and CR with HMA therapies when compared to control, but the risk of developing neutropenia, thrombocytopenia, and pneumonia was increased, confirming that HMAs are reasonable therapeutic options with a survival

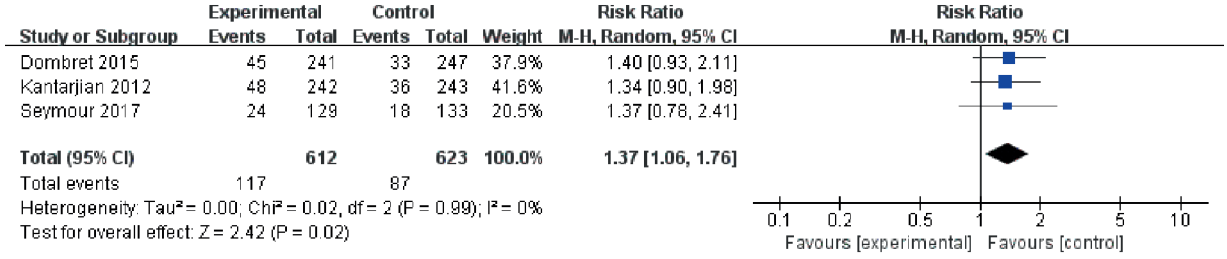

Figure 10. Forest plot of RR of pneumonia associated with HMAs *vs.* CCR or placebo.

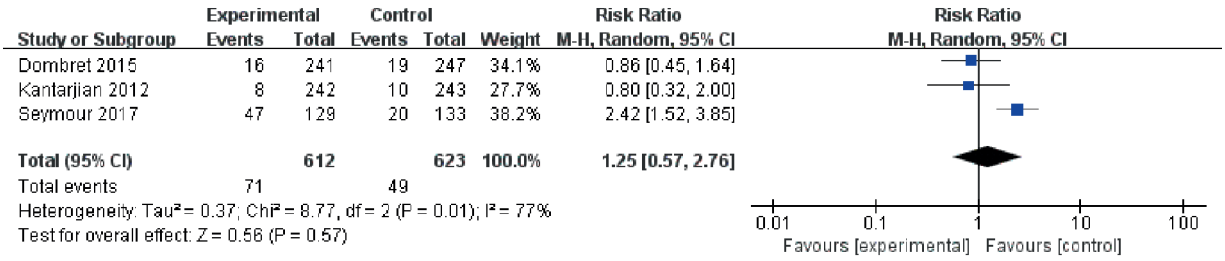

Figure 11. Forest plot of RR of leukopenia associated with HMAs *vs.* CCR or placebo.

advantage for elderly AML patients. Meanwhile, to prevent the occurrence of AEs, optimized treatment plans should be selected to achieve better clinical efficacy for demethylation therapy.

DNA methylation catalyzed by DNA methyltransferase (DNMT) is one of the most important epigenetic modifications[29,30]. In normal and cancer cells, DNA methylation modifies cytosine to regulate gene expression, while the silencing of tumor suppressor genes is related to abnormal promoter DNA methylation[31-33]. Aberrant DNA methylation is related to the prognosis and pathogenesis of AML and is regarded as the dominant mechanism of MDS progression to AML[34-36]. Nevertheless, DNA methylation can be reversed during DNA synthesis, making it a potential therapeutic target[37]. Therefore, demethylation therapy has become a routine treatment in MDS and AML[38]. Azacitidine (5-azacytidine) is metabolized to decitabine (5-aza-2′-deoxycytidine), forming a covalent protein-DNA adduct, depleting intracellular methyl-transferase, and leading to a reversal of DNA hypermethylation on tumor suppressor genes and induction of apoptosis[39,40].

Elderly AML patients have a poor physical reserve and have more comorbidities. The median OS of patients who can tolerate the CCR is about 6-8 months, and the 5-year OS rate is about 5%-15%. In elderly patients who can tolerate only LDC therapy or hydroxyurea, the median OS is only about 3-4 months, and the 2-year OS rate is about 8%-10%[41-43]. Related studies suggest that azacitidine (AZA) can prolong OS with mild side effects and is especially suitable for elderly AML patients with poor prognostic karyotypes[44]. AZA is safe and effective for elderly patients with AML and comorbidities[45], while some studies have shown that AZA significantly reduces the hospitalization rate and AEs compared with CCR[46,47]. Other studies have shown that the application of decitabine in the treatment of elderly AML has a certain effect and is well-tolerated[48-50]. The tolerance of elderly patients to demethylation drugs is significantly better than that of traditional programs, and so the development of demethylation drugs has undoubtedly brought hope to the treatment of elderly patients with AML[51].

There is currently a lack of prospective head-to-head studies on AZA and decitabine (DAC) in the treatment of AML. A retrospective study[52] showed that AZA could prolong the median OS more significantly than DAC, while the hospitalization rate in the DAC group was higher than that of in the AZA group due to infection or bleeding. This suggests that AZA is more advantageous than DAC in treating AML in elderly patients. According to a study, AZA and DAC in the treatment of MDS showed sim-

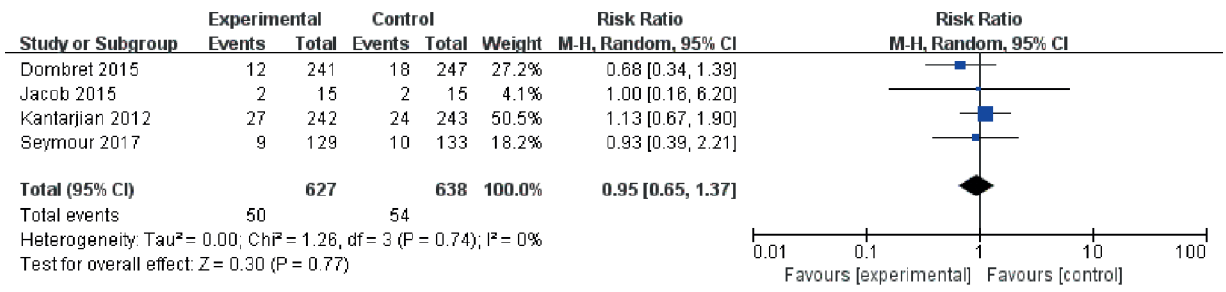

Figure 12. Forest plot of RR of hypokalemia associated with HMAs *vs.* CCR or placebo.

ilar overall efficacy results, but in the elderly patients' group (65 years or older), the survival advantage of AZA was more significant. At the same time, the incidence of AEs, such as grade 3-4 blood cell reduction and infection in the DAC group was higher[15]. Our research results confirmed that compared with CCR or placebo, AZA and DAC significantly prolonged the OS of elderly patients with AML, and there were no significant differences between the subgroups. Regarding the adverse events, HMAs demonstrated a higher incidence of neutropenia, thrombocytopenia, and pneumonia compared with CCR, which is consistent with the literature[53,54]. The incidence of anemia, febrile neutropenia, leukopenia, and hypokalemia between HMAs and CCR showed no significant differences.

As demethylation drugs are still under development, there is still a lack of molecular biomarkers that can predict whether patients might benefit from epigenetic therapy. Therefore, this paper did not involve the analysis of the effects of gene mutations and karyotype differences on the efficacy of demethylation drugs. Related research is ongoing, and some experimental studies showed that some biological indicators might be related to the responsiveness of demethylation drugs. Studies have suggested that the relatively high expression of miR-29b, miR-29c, and miR-181 is related to the clinical response rate of decitabine in treating AML in elderly patients[55,56]. At the same time, Metzeler et al[57] showed that AML patients with low DNMT3A expression might benefit from demethylation drug treatment. Furthermore, if leukemia relapses in AML patients or was refractory to HMA, usually HMAs or other low-intensity therapies that have a dismal prognosis were continued. A multicenter historical prospective study found that the addition of venetoclax (a BCL-2 inhibitor) to AML patients who previously failed HMA might overcome resistance[58] and demonstrated superior response and prolonged survival[59]. Especially in FLT3-mutated (FLT3m) AML patients, the combined use of venetoclax and HMAs showed encouraging efficacy[60]. These might provide new ideas for targeted therapy of epigenetics.

However, there are several limitations in the current analysis. Firstly, significant heterogeneity was observed in the CR analysis (I^2=69 %, p=0.006). The primary source of heterogeneity was from Dombret[24], and the CR rate in the AZA group was lower than that in the CCR group (19.5% *vs.* 21.9%), but the morphologic CR with incomplete blood count recovery was higher (8.3% *vs.* 3.2%) in this study. Secondly, most of the included studies were not blinded, and the allocation concealment was not clear, which led to increased bias. Thirdly, this study lacked multicenter, large-sample studies. Finally, some unpublished negative results were not included.

A second-generation HMA has been developed to reduce the elimination of decitabine by cytidine deaminase, thereby increasing the *in vivo* exposure of decitabine. A recent clinical trial with Guadecitabine (SGI-110, dinucleotide of decitabine and deoxyguanosine) demonstrated a comparable safety profile to decitabine with a significantly longer half-life[61]. A phase II clinical trial showed that more than half of the elderly treatment-naive patients with AML achieved a composite CR with guadecitabine and tolerable toxicity[62]. Double-blind RCTs should be carried out to confirm the toxicity and efficacy of SGI-110 in the future.

Conclusions

In summary, this study aimed to identify if HMAs have therapeutic advantages compared with CCR or placebo in elderly AML patients. The results showed that in the analysis of prospective RCTs in elderly patients with AML, HMAs showed improved response rates and OS in comparison to CCR or placebo. Although HMAs are associated with a higher incidence of AEs such as neutropenia, thrombocytopenia, and pneumonia, demethylation drugs were well-tolerated in the treatment of elderly AML. The factors affecting the reactivity of demethylated drugs need continuous exploration. Therefore, this meta-analysis suggests that although HMAs cause a higher incidence of adverse events such as neutropenia, thrombocytopenia, and pneumonia, demethylation drugs are well-tolerated and effective for treating AML in the elderly.

Author Contributions

(I) Conception and design: Rui-Juan Zhang, Lin-Hua Yang; (II) Administrative support: Lin-Hua Yang; (III) Provision of study materials or patients: Zhi-Juan Zhang; (IV) Collection and assembly of data: Jia-Hong Zhai; (V) Data analysis and interpretation: Mei-Fang Wang, Chun-Xia Dong; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Sources of Support
This study was not supported by any financial sources.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Reporting Checklist
The authors have completed the PRISMA 2009 checklist.

Data Sharing Statement
Not applicable.

Acknowledgments
The authors would like to thank all study participants who were enrolled in this study.

Ethical Statement
This study was based on previously published studies; therefore, ethical approval and patient consent are not relevant.

References

1) Shallis RM, Wang R, Davidoff A, Ma X, Zeidan AM. Epidemiology of acute myeloid leukemia: Recent progress and enduring challenges. Blood Rev 2019; 36: 70-87.
2) Milano AF. 20-Year Comparative Survival and Mortality of Cancer of the Stomach by Age, Sex, Race, Stage, Grade, Cohort Entry Time-Period, Disease Duration & Selected ICD-O-3 Oncologic Phenotypes: A Systematic Review of 157,258 Cases for Diagnosis Years 1973-2014: (SEER*Stat 8.3.4). J Insur Med 2019; 48: 5-23.
3) Krug U, Büchner T, Berdel WE, Müller-Tidow C. The treatment of elderly patients with acute myeloid leukemia. Dtsch Arztebl Int 2011; 108: 863-870.
4) Burnett A, Wetzler M, Löwenberg B. Therapeutic advances in acute myeloid leukemia. J Clin Oncol 2011; 29: 487-494.
5) Döhner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. N Engl J Med 2015; 373: 1136-1152.
6) Bose P, Vachhani P, Cortes JE. Treatment of Relapsed/Refractory Acute Myeloid Leukemia. Curr Treat Options Oncol 2017; 18: 17.
7) Daly MC, Paquette IM. Surveillance, Epidemiology, and End Results (SEER) and SEER-Medicare Databases: Use in Clinical Research for Improving Colorectal Cancer Outcomes. Clin Colon Rectal Surg 2019; 32: 61-68.
8) Kantarjian H, O'Brien S, Cortes J, Giles F, Faderl S, Jabbour E, Garcia-Manero G, Wierda W, Pierce S, Shan J, Estey E. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome. Cancer 2006; 106: 1090-1098.
9) Thol F, Schlenk RF, Heuser M, Ganser A. How I treat refractory and early relapsed acute myeloid leukemia. Blood 2015; 126: 319-327.
10) Witkowski MT, Lasry A, Carroll WL, Aifantis I. Immune-Based Therapies in Acute Leukemia. Trends Cancer 2019; 5: 604-618.
11) Issa JP. The myelodysplastic syndrome as a prototypical epigenetic disease. Blood 2013; 121: 3811-3817.
12) Schoofs T, Berdel WE, Müller-Tidow C. Origins of aberrant DNA methylation in acute myeloid leukemia. Leukemia 2014; 28: 1-14.
13) Di Croce L, Raker VA, Corsaro M, Fazi F, Fanelli M, Faretta M, Fuks F, Lo Coco F, Kouzarides T, Nervi C, Minucci S, Pelicci PG. Methyltransferase recruitment and DNA hypermethylation of target promoters by an oncogenic transcription factor. Science 2002; 295: 1079-1082.
14) Acute myeloid leukemia (version 2.2018). 2018. (Accessed 20/07/2020, 2020)
15) Lee YG, Kim I, Yoon SS, Park S, Cheong JW, Min YH, Lee JO, Bang SM, Yi HG, Kim CS, Park Y, Kim BS, Mun YC, Seong CM, Park J, Lee JH, Kim SY, Lee HG, Kim YK, Kim HJ. Comparative analysis between azacitidine and decitabine for the treatment of myelodysplastic syndromes. Br J Haematol 2013; 161: 339-347.
16) Lee JH, Choi Y, Kim SD, Kim DY, Lee JH, Lee KH, Lee SM, Cho SH, Lee WS, Joo YD. Comparison of 7-day azacitidine and 5-day decitabine for treating myelodysplastic syndrome. Ann Hematol 2013; 92: 889-897.
17) Tawfik B, Sliesoraitis S, Lyerly S, Klepin HD, Lawrence J, Isom S, Ellis LR, Manuel M, Dralle S, Berenzon D, Powell BL, Pardee T. Efficacy of the hypomethylating agents as frontline, salvage, or consolidation therapy in adults with acute myeloid leukemia (AML). Ann Hematol 2014; 93: 47-55.
18) Gardin C, Dombret H. Hypomethylating Agents as a Therapy for AML. Curr Hematol Malig Rep 2017; 12: 1-10.
19) Fenaux P, Mufti GJ, Hellström-Lindberg E, Santini V, Gattermann N, Germing U, Sanz G, List AF, Gore S, Seymour JF, Dombret H, Backstrom J, Zimmerman L, McKenzie D, Beach CL, Silverman LR. 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: 562-569.
20) Jacob LA, Aparna S, Lakshmaiah KC, Lokanatha D, Babu G, Babu S, Appachu S. 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.
21) Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and

meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 350: g7647.
22) Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019; 10: Ed000142.
23) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.
24) Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, Kumar R, Cavenagh J, Schuh AC, Candoni A, Récher C, Sandhu I, Bernal del Castillo T, Al-Ali HK, Martinelli G, Falantes J, Noppeney R, Stone RM, Minden MD, McIntyre H, Songer S, Lucy LM, Beach CL, Döhner H. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 2015; 126: 291-299.
25) Huls G, Chitu DA, Havelange V, Jongen-Lavrencic M, van de Loosdrecht AA, Biemond BJ, Sinnige H, Hodossy B, Graux C, Kooy RVM, de Weerdt O, Breems D, Klein S, Kuball J, Deeren D, Terpstra W, Vekemans MC, Ossenkoppele GJ, Vellenga E, Löwenberg B. Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients. Blood 2019; 133: 1457-1464.
26) Seymour JF, Döhner H, Butrym A, Wierzbowska A, Selleslag D, Jang JH, Kumar R, Cavenagh J, Schuh AC, Candoni A, Récher C, Sandhu I, Del Castillo TB, Al-Ali HK, Falantes J, Stone RM, Minden MD, Weaver J, Songer S, Beach CL, Dombret H. Azacitidine improves clinical outcomes in older patients with acute myeloid leukaemia with myelodysplasia-related changes compared with conventional care regimens. BMC Cancer 2017; 17: 852.
27) Wei A, Döhner H, Pocock C, Montesinos P, Afanasyev B, Dombret H, Ravandi F, Sayar H, Jang J, Porkka K, Selleslag D, Sandhu I, Turgut M, Giai V, Ofran Y, Çakar M, Sousa A, Rybka J, Frairia C, Roboz G. The QUAZAR AML-001 Maintenance Trial: Results of a Phase III International, Randomized, Double-Blind, Placebo-Controlled Study of CC-486 (Oral Formulation of Azacitidine) in Patients with Acute Myeloid Leukemia (AML) in First Remission. Blood 2019; 134: LBA-3.
28) Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, Gau JP, Chou WC, Buckstein R, Cermak J, Kuo CY, Oriol A, Ravandi F, Faderl S, Delaunay J, Lysák D, Minden M, Arthur C. 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: 2670-2677.
29) Hashimoto H, Vertino PM, Cheng X. Molecular coupling of DNA methylation and histone methylation. Epigenomics 2010; 2: 657-669.
30) Jeltsch A, Gowher H. Editorial-Role of DNA Methyltransferases in the Epigenome. Genes (Basel) 2019; 10.
31) Pan Y, Liu G, Zhou F, Su B, Li Y. DNA methylation profiles in cancer diagnosis and therapeutics. Clin Exp Med 2018; 18: 1-14.
32) Klutstein M, Nejman D, Greenfield R, Cedar H. DNA methylation in cancer and aging. Cancer Res 2016; 76: 3446-3450.
33) Kulis M, Esteller M. DNA methylation and cancer. Adv Genet 2010; 70: 27-56.
34) Grövdal M, Khan R, Aggerholm A, Antunovic P, Astermark J, Bernell P, Engström LM, Kjeldsen L, Linder O, Nilsson L, Olsson A, Wallvik J, Tangen JM, Oberg G, Jacobsen SE, Hokland P, Porwit A, Hellström-Lindberg E. Negative effect of DNA hypermethylation on the outcome of intensive chemotherapy in older patients with high-risk myelodysplastic syndromes and acute myeloid leukemia following myelodysplastic syndrome. Clin Cancer Res 2007; 13: 7107-7112.
35) Benetatos L, Vartholomatos G. Enhancer DNA methylation in acute myeloid leukemia and myelodysplastic syndromes. Cell Mol Life Sci 2018; 75: 1999-2009.
36) Jiang Y, Dunbar A, Gondek LP, Mohan S, Rataul M, O'Keefe C, Sekeres M, Saunthararajah Y, Maciejewski JP. Aberrant DNA methylation is a dominant mechanism in MDS progression to AML. Blood 2009; 113: 1315-1325.
37) Jabłońska E, Reszka E. Selenium and Epigenetics in Cancer: Focus on DNA Methylation. Adv Cancer Res 2017; 136: 193-234.
38) van der Helm LH, Scheepers ER, Veeger NJ, Daenen SM, Mulder AB, van den Berg E, Vellenga E, Huls G. Azacitidine might be beneficial in a subgroup of older AML patients compared to intensive chemotherapy: a single centre retrospective study of 227 consecutive patients. J Hematol Oncol 2013; 6: 29.
39) Zhou Z, Li HQ, Liu F. DNA Methyltransferase Inhibitors and their Therapeutic Potential. Curr Top Med Chem 2018; 18: 2448-2457.
40) Christman JK. 5-Azacytidine and 5-aza-2'-deoxycytidine as inhibitors of DNA methylation: mechanistic studies and their implications for cancer therapy. Oncogene 2002; 21: 5483-5495.
41) Webster JA, Pratz KW. Acute myeloid leukemia in the elderly: therapeutic options and choice. Leuk Lymphoma 2018; 59: 274-287.
42) Klepin HD. Elderly acute myeloid leukemia: assessing risk. Curr Hematol Malig Rep 2015; 10: 118-125.
43) Appelbaum FR, Gundacker H, Head DR, Slovak ML, Willman CL, Godwin JE, Anderson JE, Petersdorf SH. Age and acute myeloid leukemia. Blood 2006; 107: 3481-3485.
44) Schuh AC, Döhner H, Pleyer L, Seymour JF, Fenaux P, Dombret H. Azacitidine in adult patients with acute myeloid leukemia. Crit Rev Oncol Hematol 2017; 116: 159-177.
45) Pleyer L, Döhner H, Dombret H, Seymour JF, Schuh AC, Beach CL, Swern AS, Burgstaller S, Stauder R, Girschikofsky M, Sill H, Schlick K, Thaler J, Halter B, Machherndl Spandl S, Zebisch A, Pichler A, Pfeilstöcker M, Autzinger EM, Lang

A, Geissler K, Voskova D, Sperr WR, Hojas S, Rogulj IM, Andel J, Greil R. Azacitidine for frontline therapy of patients with AML: reproducible efficacy established by direct comparison of international phase 3 trial data with registry data from the Austrian azacitidine registry of the AGMT study group. Int J Mol Sci 2017; 18: 415.
46) Lao Z, Yiu R, Wong GC, Ho A. Treatment of elderly patients with acute myeloid leukemia with azacitidine results in fewer hospitalization days and infective complications but similar survival compared with intensive chemotherapy. Asia Pac J Clin Oncol 2015; 11: 54-61.
47) Seymour JF, Döhner H, Minden MD, Stone R, Gambini D, Dougherty D, Beach CL, Weaver J, Dombret H. Incidence rates of treatment-emergent adverse events and related hospitalization are reduced with azacitidine compared with conventional care regimens in older patients with acute myeloid leukemia. Leuk Lymphoma 2017; 58: 1412-1423.
48) 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: 556-561.
49) Park H, Chung H, Lee J, Jang J, Kim Y, Kim SJ, Kim JS, Min YH, Cheong JW. Decitabine as a First-Line Treatment for Older Adults Newly Diagnosed with Acute Myeloid Leukemia. Yonsei Med J 2017; 58: 35-42.
50) Lübbert M, Rüter BH, Claus R, Schmoor C, Schmid M, Germing U, Kuendgen A, Rethwisch V, Ganser A, Platzbecker U, Galm O, Brugger W, Heil G, Hackanson B, Deschler B, Döhner K, Hagemeijer A, Wijermans PW, Döhner H. 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.
51) Al-Ali HK, Jaekel N, Niederwieser D. The role of hypomethylating agents in the treatment of elderly patients with AML. J Geriatr Oncol 2014; 5: 89-105.
52) Smith BD, Beach CL, Mahmoud D, Weber L, Henk HJ. Survival and hospitalization among patients with acute myeloid leukemia treated with azacitidine or decitabine in a large managed care population: a real-world, retrospective, claims-based, comparative analysis. Exp Hematol Oncol 2014; 3: 10.
53) Gao C, Wang J, Li Y, Zhao H, Li R, Hou L, Zhang Y, Tian S, Liang H, Wang C, Chen X, Wang J. Incidence and risk of hematologic toxicities with hypomethylating agents in the treatment of myelodysplastic syndromes and acute myeloid leukopenia: a systematic review and meta-analysis. Medicine (Baltimore) 2018; 97: e11860.
54) Yun S, Vincelette ND, Abraham I, Robertson KD, Fernandez-Zapico ME, Patnaik MM. Targeting epigenetic pathways in acute myeloid leukemia and myelodysplastic syndrome: a systematic review of hypomethylating agents trials. Clin Epigenetics 2016; 8: 68.
55) Butrym A, Rybka J, Baczyńska D, Poręba R, Kuliczkowski K, Mazur G. Clinical response to azacitidine therapy depends on microRNA-29c (miR-29c) expression in older acute myeloid leukemia (AML) patients. Oncotarget 2016; 7: 30250-30257.
56) Blum W, Garzon R, Klisovic RB, Schwind S, Walker A, Geyer S, Liu S, Havelange V, Becker H, Schaaf L, Mickle J, Devine H, Kefauver C, Devine SM, Chan KK, Heerema NA, Bloomfield CD, Grever MR, Byrd JC, Villalona-Calero M, Croce CM, Marcucci G. Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. Proc Natl Acad Sci U S A 2010; 107: 7473-7478.
57) Metzeler KH, Walker A, Geyer S, Garzon R, Klisovic RB, Bloomfield CD, Blum W, Marcucci G. DNMT3A mutations and response to the hypomethylating agent decitabine in acute myeloid leukemia. Leukemia 2012; 26: 1106-1107.
58) Ram R, Amit O, Zuckerman T, Gurion R, Raanani P, Bar-On Y, Avivi I, Wolach O. Venetoclax in patients with acute myeloid leukemia refractory to hypomethylating agents-a multicenter historical prospective study. Ann Hematol 2019; 98: 1927-1932.
59) Morsia E, McCullough K, Joshi M, Cook J, Alkhateeb HB, Al-Kali A, Begna K, Elliott M, Hogan W, Litzow M, Shah M, Pardanani A, Patnaik M, Tefferi A, Gangat N. Venetoclax and hypomethylating agents in acute myeloid leukemia: Mayo Clinic series on 86 patients. Am J Hematol 2020; 95: 1511-1521.
60) Aldoss I, Zhang J, Mei M, Al Malki MM, Arslan S, Ngo D, Aribi A, Ali H, Sandhu K, Salhotra A, Koller P, Khaled S, Artz A, Snyder D, Nakamura R, Forman SJ, Stein AS, Marcucci G, Pullarkat V. Venetoclax and hypomethylating agents in FLT3-mutated acute myeloid leukemia. Am J Hematol. 2020 Jul 6. doi: 10.1002/ajh.25929. Epub ahead of print.
61) Issa JJ, Roboz G, Rizzieri D, Jabbour E, Stock W, O'Connell C, Yee K, Tibes R, Griffiths EA, Walsh K, Daver N, Chung W, Naim S, Taverna P, Oganesian A, Hao Y, Lowder JN, Azab M, Kantarjian H. Safety and tolerability of guadecitabine (SGI-110) in patients with myelodysplastic syndrome and acute myeloid leukaemia: a multicentre, randomised, dose-escalation phase 1 study. Lancet Oncol 2015; 16: 1099-1110.
62) Kantarjian HM, Roboz GJ, Kropf PL, Yee KWL, O'Connell CL, Tibes R, Walsh KJ, Podoltsev NA, Griffiths EA, Jabbour E, Garcia-Manero G, Rizzieri D, Stock W, Savona MR, Rosenblat TL, Berdeja JG, Ravandi F, Rock EP, Hao Y, Azab M, Issa JJ. Guadecitabine (SGI-110) in treatment-naive patients with acute myeloid leukaemia: phase 2 results from a multicentre, randomised, phase 1/2 trial. Lancet Oncol 2017; 18: 1317-1326.