INPLASY

Effect of Hypomethylating Agents on Prognosis in Acute Myeloid Leukemia Patients Treated with HAG Priming

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 July 2024 and was last updated on 22 July 2024.

INTRODUCTION

Review question / Objective A combination of hypomethylation agents (HMAs) and the HAG regimen (homoharringtonine, cytarabine, G-CSF) holds promise as a treatment for Acute Myeloid Leukemia (AML). However, the clinical efficacy of this treatment compared to the HAG regimen remains unclear. We conducted a meta-analysis of eligible studies comparing the clinical efficacy of the two regimens.

Condition being studied Acute Myeloid Leukemia (AML) is a serious blood cancer characterized by the uncontrolled proliferation of abnormal myeloid cells in the bone marrow and peripheral blood. These abnormal cells interfere with the production of normal blood cells, leading to symptoms such as anemia, infection, and bleeding. Despite advancements in chemotherapy, the prognosis for AML patients, particularly the elderly, those ineligible for intensive treatments, and those with relapsed or refractory disease, remains poor. Therefore, there is a pressing need for novel treatment strategies to improve clinical outcomes for AML patients. In this context, hypomethylation agents (HMAs) have emerged as a promising therapeutic option, with increasing evidence suggesting their efficacy when combined with other agents like Homoharringtonine, Cytarabine, and Granulocyte Colony-Stimulating Factor (HAG). However, the comparative clinical efficacy of HMAs plus HAG versus HAG alone remains to be fully elucidated.

METHODS

Search strategy A comprehensive literature search of PubMed, Cochrane and CNKI (China) databases for studies comparing the clinical efficacy of the azacitidine plus HAG regimen with the HAG regimen in treating AML patients. Our search covered all records from the inception of these databases up to March 2023, with no language restrictions. Our search terms included "acute myeloid leukemia," "AML," "Azacitidine," "DACitabine," "HAG regimen," "homoharringtonine," "cytarabine," and

"granulocyte colony-stimulating factor." Additionally, we scanned the references of relevant studies to identify additional studies.

Participant or population Newly diagnosed AML (elderly patients [over 60 years] or ineligible for receiving intensive chemotherapy [IC]) and relapsed/refractory AML.

Intervention Inclusion criteria: (1) studies that reported the clinical efficacy of HMAs (Azacitidine or Decitabine) plus HAG regimen (Homoharringtonine, cytarabine and G-CSF) in newly diagnosed AML (elderly patients [over 60 years] or ineligible for receiving intensive chemotherapy [IC]) and relapsed/refractory AML; (2) studies that reported outcomes such as complete remission (CR) or with incomplete peripheral blood recovery (CRi), overall response rate (ORR), overall survival (OS), and relapse-free survival (RFS); (3) studies with full-text availability. We excluded case reports, reviews, letters, conference abstracts, or studies that lacked relevant data.
Exclusion criteria: studies that only reported the clinical efficacy in AML-M3, myelodysplastic syndrome (MDS) or AML patients with ECOG score ≤2 were excluded.

Comparator Inclusion criteria: (1) studies that reported the clinical efficacy of mono- HAG regimen (Homoharringtonine, cytarabine and G-CSF) in newly diagnosed AML (elderly patients [over 60 years] or ineligible for receiving intensive chemotherapy [IC]) and relapsed/refractory AML; (2) studies that reported outcomes such as complete remission (CR) or with incomplete peripheral blood recovery (CRi), overall response rate (ORR), overall survival (OS), and relapse-free survival (RFS); (3) studies with full-text availability. We excluded case reports, reviews, letters, conference abstracts, or studies that lacked relevant data.
Exclusion criteria: studies that only reported the clinical efficacy in AML-M3, myelodysplastic syndrome (MDS) or AML patients with ECOG score ≤2 were excluded.

Study designs to be included We will include randomised trials or single arm trial to assess the beneficial effects of the treatments, and will supplement these with observational studies (including cohort and case–control studies) for the assessment of harms. Preclinical studies, case reports, unpublished results will be excluded.

Eligibility criteria We included studies that met the following criteria: (1) studies that reported the clinical efficacy of HMAs plus HAG/Mono HAG regimen in newly diagnosed AML (elderly patients [over 60 years] or ineligible for receiving intensive chemotherapy [IC]) and relapsed/refractory AML; (2) studies that reported outcomes such as complete remission (CR) or with incomplete peripheral blood recovery (CRi), overall response rate (ORR), overall survival (OS), and relapse-free survival (RFS); (3) studies with full-text availability. We excluded case reports, reviews, letters, conference abstracts, or studies that lacked relevant data. Preclinical studies, case reports, and studies that only reported the clinical efficacy in myelodysplastic syndrome (MDS) were excluded.

Information sources Electronic databases: CNKI, CochraneLibrary, Pubmed and Embase.

Main outcome(s) Complete remission (CR) or with incomplete peripheral blood recovery (CRi), overall response rate (ORR), overall survival (OS), and relapse-free survival (RFS).

Additional outcome(s) Not applicable.

Data management
1.Study Selection
2 reviewer will select studies for inclusion in the systematic review.
Selection Process: Two individuals will independently screen records for inclusion.
Blinding: Researchers will be blinded to each other's decisions to minimize any potential bias that may arise from knowledge of another reviewer's selections.

Disagreements Resolution: Any disagreements between individual judgements will be resolved through a third reviewer will be consulted to make the final decision.

Recording System: using R software system.
2.Data Extraction
Data to be Extracted:
Study design and methodology
Participant demographics and baseline characteristics
Numbers of events or measures of effect (where applicable)
Any additional relevant data as per the review protocol

Obtaining Data: If certain data points are not explicitly reported in the study documents, study investigators will be contacted for unreported data or additional details.

Number of People Involved: 2 individuals will be involved in the extraction or checking of data to ensure accuracy and consistency.

Extraction Process: Data will be extracted independently by two people, and then cross-checked to resolve any discrepancies. If one person extracts data, another will check the extracted data for accuracy.

Disagreements Resolution: Disagreements in data extraction will be resolved through a third party will be involved to verify the data.

Handling Missing Data: Missing data will be addressed by contacting study investigators for clarification or additional details. If the data cannot be obtained, it will be clearly documented and the reasons for the absence noted.

Recording Data: Data will be recorded in a systematic manner, using tools such as an Excel spreadsheet or R software.
Software or Tool: The R software will be used for data extraction and management. This software will facilitate the organization and analysis of the extracted data, making the review process more efficient and reliable.

Quality assessment / Risk of bias analysis

1. Characteristics to be Assessed:
Randomization Methods: The appropriateness of the randomization process will be evaluated.
Treatment Allocation: The measures taken to ensure the concealment of allocation will be checked, such as centralized randomization systems.
Blinding: The implementation of blinding in the study, including participant, personnel, and outcome assessor blinding, will be assessed.

2. Level of Assessment:
It will be determined whether the assessment will be conducted at the study level or the outcome level. Typically, assessments are conducted at the outcome level, but sometimes they are also conducted at the study level to evaluate the overall quality of the study design.

3. Criteria for Assessing Internal Validity:
ROBINS-I: Used for assessing the risk of bias in non-randomized intervention studies.

4.How the Results of the Assessment Will Inform Data Synthesis:
The impact of the assessment results on the synthesis of study findings will be explained.

5. Number of Reviewers Involved in Quality Assessment:
The number of reviewers who will be involved in the quality assessment will be determined. Typically, at least two reviewers independently conduct the assessment to increase reliability.

6. Resolution of Disagreements Between Reviewers' Judgments:
A third reviewer is brought in to resolve the disagreement.

Strategy of data synthesis

Criteria for Data Synthesis

1. Minimum Number of Studies: The synthesis will be conducted only if a minimum of five studies are included in the review. This threshold is chosen to ensure sufficient data for a robust analysis.
2. Level of Consistency: Data will be synthesized if there is a high level of consistency in the outcomes measured across studies. This will be assessed based on the similarity of study designs, interventions, and outcome measures.

#Data to be Synthesized

1. Outcomes: The primary outcomes of interest will include complete remission (CR) or with incomplete peripheral blood recovery (CRi), overall response rate (ORR), progression-free survival at 2 years, overall survival (OS), and relapse-free survival (RFS).
2. Summary Effect Measures: Risk ratios will be calculated for binary outcomes such as relapse-free survival and overall survival.

#Formal Method of Combining Individual Study Data

1. Statistical Models: A random-effects meta-analysis will be used to combine individual study data. This method is chosen because it accounts for both within-study and between-study variability, providing a more comprehensive estimate of the effect.
2. Assessment of Heterogeneity: Heterogeneity will be assessed using the I^2 statistic and the Cochran's Q test. A high level of heterogeneity ($I^2 > 50\%$) will prompt further investigation into potential sources of variability, such as differences in study populations, interventions, or outcome measures.
3. Subgroup Analyses: If significant heterogeneity is detected, subgroup analyses will be conducted based on factors such as age, disease stage, or treatment type.

4. Sensitivity Analyses：Sensitivity analyses will be performed to assess the robustness of the findings.
5. Publication Bias: Publication bias will be assessed using funnel plots and statistical tests such as Egger's test. If publication bias is detected, it will be addressed in the discussion of the review findings.

#Methods of Synthesizing Qualitative Data

1. Thematic Analysis: Qualitative data will be synthesized using thematic analysis.
2. **Narrative Synthesis: A narrative synthesis will be used to integrate the findings of qualitative studies.

#Software for Data Synthesis

1. Statistical Software: Statistical software such as R (with packages like metafor) or Stata will be used for the meta-analysis and other statistical analyses.

Subgroup analysis NA.

Sensitivity analysis NA.

Country(ies) involved China.

Other relevant information NA.

Keywords Acute Myeloid Leukemia, hypomethylation agents, Azacitidine, Decitabine, HAG regimen, Meta-Analysis.

Contributions of each author

Author 1 - Jun Li - Author 1 conceived and designed the study.
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