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Efficacy and safety of second-generation FLT3 Inhibitors in acute myeloid leukemia: a systematic review and meta-analysis of randomized controlled trials

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ADMINISTRATIVE INFORMATION

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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 31 May 2024 and was last updated on 31 May 2024.

INTRODUCTION

Review question / Objective To evaluate the efficacy and safety of second-generation FLT3 inhibitors in the treatment of acute myeloid leukemia.

Rationale FLT3 inhibitors, a class of tyrosine kinase inhibitors, are divided into first and second generations. However, studies comparing the efficacy of second-generation FLT3 inhibitors in AML treatment are scarce. This meta-analysis aimed to evaluate the clinical efficacy and safety of second-generation FLT3 inhibitors.

Condition being studied The PICO (population, intervention, comparison, outcome) framework for this meta-analysis was defined as follows: P: human participants with AML and FLT3 mutations; I: treatment with second-generation FLT3 inhibitors; C: control group.

METHODS

Search strategy Two authors (T.-S.W. and S.-Y.H.) independently conducted a thorough screening and assessment of each study. The search included PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov using the keywords "Quizartinib OR AC220," "Gilteritinib OR ASP2215," and "Acute Myeloid Leukemia" from the earliest records up to April 28, 2024.

Participant or population Human participants with AML and FLT3 mutations.

Intervention Treatment with second-generation FLT3 inhibitors.

Comparator Control.

Study designs to be included Randomized controlled trials.

Eligibility criteria We manually reviewed the reference lists of relevant articles to identify additional eligible papers. There were no language restrictions applied, and studies meeting the following criteria were included: (1) inclusion of patients diagnosed with AML; (2) use of a second FLT3 inhibitor as either monotherapy or in combination with other chemotherapy as the intervention;(3) reporting of study outcomes related to overall survival; and (4) reporting of study outcomes related to QTc prolongation or cardiovascular disorders.

Information sources Two authors (T.-S.W. and S.-Y.H.) independently conducted a thorough screening and assessment of each study. The search included PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov using the keywords "Quizartinib OR AC220," "Gilteritinib OR ASP2215," and "Acute Myeloid Leukemia" from the earliest records up to April 28, 2024.

Main outcome(s) The primary outcome assessed in this study was the overall survival efficacy of second-generation FLT3 inhibitors.

Additional outcome(s) Secondary outcomes included the risk of cardiovascular events, such as atrial fibrillation, cardiac failure, cardiac arrest, myocardial infarction, acute myocardial infarction, and prolonged QT interval on Electrocardiogram, as well as common adverse events such as anemia, neutropenia, thrombocytopenia, diarrhea, and pneumonia.

Data management Data extraction from the evaluated studies was performed independently by two authors (T.-S.W. and S.-Y.H.). Each study provided the following data: the name of the first author, the publication year, participant demographics including age, sample size, the specific second-generation FLT3 inhibitor used in treatment, outcome measures, efficacy in terms of overall survival, and data on the risk of cardiovascular events and electrocardiogram QT prolongation, anemia, neutropenia, thrombocytopenia, diarrhea, and pneumonia.

Quality assessment / Risk of bias analysis To assess the methodological quality of the included studies, we employed the Cochrane risk of bias tool for randomized trials (version 2, RoB 2, London,United Kingdom). This tool comprises six key domains for evaluating study quality: randomization process, adherence to intervention, handling of missing outcome data, outcome measurement, selective reporting, and overall risk of bias.

Strategy of data synthesis Due to the heterogeneity in the types of second-generation FLT3 inhibitors used across the included studies, we employed a random-effects model for the meta-analysis, which was conducted using Comprehensive Meta-Analysis software (version 4,Biostat, Englewood, NJ, United States). Statistical significance was defined as a two-tailed p-value of less than 0.05. Hazard ratios with 95% confidence intervals (CIs) were employed to quantify the primary study outcomes, while odds ratios (ORs) with their corresponding 95% CIs were analyzed for the secondary outcomes. I 2 was also assessed to determine the extent of heterogeneity among the studies. I 2 values of 25%,50%, and 75% were considered indicative of low, moderate, and high heterogeneity, respectively.

Subgroup analysis Subgroup analyses based on the type of AML and the specific second-generation FLT3 inhibitor used. Meta-regression analyses to investigate the potential association between treatment effects related to age and overall survival outcomes.

Sensitivity analysis To ensure the reliability of our meta-analysis, sensitivity analyses were conducted using the one-study removal approach. This method helped ascertain whether the summary effect size experienced a statistically significant alteration upon the exclusion of any specific trial from the analysis.

Language restriction No language limit.

Country(ies) involved Taiwan.

Keywords Second-generation FLT3 inhibitors, Gilteritinib, Quizartinib, Overall survival, ProlongedQTc interval.

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