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Meta-analysis of the effect of FLT3 inhibitor maintenance therapy on survival and chronic graft-versus-host disease in allogeneic hematopoietic stem cell transplantation for malignant hematologic disease

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ABSTRACT

This study aimed to investigate the effect of FLT3 inhibitor maintenance therapy on survival and chronic graft-versus-host diseases (cGVHD) in allogeneic hematopoietic stem cell transplantation (allo-HSCT) for malignant hematologic disease (MHD) by meta-analysis. For this purpose, Pubmed, Web of Science, Embase, and The Cochrane Library were searched for studies published up to April 2023. The search term was set as "FLT3 inhibitor". "allogeneic hematopoietic stem cell transplantation"; "malignant hematologic disease"; "chronic graft-versus-host disease". The literature was screened according to the inclusion and exclusion criteria, and then the data were extracted and analyzed by Revman5.3 software. Results showed that 9 eligible studies involving 964 patients were obtained. The relapse-free survival (RFS) of patients after treatment was analyzed by comprehensive model, odds ratio=3.28, 95% confidence interval (CI) = 1.76-6.11, Z=3.75, P=0.0002; Comprehensive model analysis of overall survival (OS), odds ratio=2.85, 95% CI= 2.12-3.83, Z=6.95, P <0.00001; Comprehensive model analysis of cGVHD, odds ratio=1.06, 95%CI = 0.37-2.98, Z=0.11, P=0.92. It was concluded that FLT3 inhibitor maintenance therapy could improve the RFS and OS of MHD patients treated with allo-HSCT but did not markedly affect the occurrence of cGVHD.

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Introduction

MHD refers to occur in the hematopoietic system and hematopoietic tissue and organs of a group of Malignant tumor diseases, mostly malignant hematopoietic stem cells cloned disease (1). According to the source of occurrence, it can be divided into leukemia (including acute and chronic leukemia) (2); plasma cell tumors (including multiple myeloma, macroglobulinemia, etc.) (3); lymphoma (including Hodgkin lymphoma, non-Hodgkin lymphoma) (4); and malignant histiocytosis, myeloproliferative diseases (including myelodysplastic syndrome, essential thrombocythemia, polycythemia vera, primary myelofibrosis) (5). Allo-HSCT is very popular in clinical applications and is a curative treatment for hematological diseases (6). With the improvement of the medical level, the number of HSCT patients and one-year survival rate after surgery have been greatly improved. The progress of allo-HSCT makes "everyone has a source of stem cells", and allogeneic transplantation is now more common in clinical practice (7). With the development of transplantation technology, stem cell sources, and instruments and facilities, its application scope continues to expand, and the number of transplants continues to rise.

However, a series of complications such as disease recurrence, preconditioning-related toxicity, long-term immunodeficiency and infection, and graft-versus-host disease (GVHD) can occur after allo-HSCT, which have a serious impact on the long-term survival of patients (8,9). GVHD is one of the factors that have the greatest impact on the success or failure of transplantation and prognosis among the many known transplant complications (10). Transplanted cells treat the recipient host as alien and mediate immune damage, which is immune rejection caused by donor T cells recognizing host antigens, which directly affects the survival rate of patients after transplantation. In hematopoietic stem cell transplantation, there are two types: acute GVHD (aGVHD) and cGVHD(11,12). aGVHD occurs 100 days before hematopoietic stem cell transplantation. T cells recognize the host polypeptide major histocompatibility complex and minor histocompatibility complex, which are caused by T cells and helper T cells, and amplified by cytokine linkage. The target organs are mainly skin, liver and gastrointestinal tract, with pathological features of "satellite cell necrosis" accompanied by hyalinization of epithelial basal cells (13). cGVHD usually occurs 100 days after hematopoietic stem cell transplantation and T cells recognize the host major histocompatibility complex type II molecular determinants. The main complication of cGVHD is infection, which is a common cause of death in patients with cGVHD and involves multiple organs of the whole body. The pathological features are liver invasive hepatitis, bridging necrosis, gastrointestinal crypt destruction, lamina propria fibrosis, thickening and hyperkeratosis of the skin epidermal spinous layer, Howell-Jolly bodies in peripheral blood smears, etc. (14).

The FLT3 gene belongs to the receptor tyrosine kinase class III subfamily (FLT3, KIT, FMS, and PDGFR), which

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is located on chromosome 13q12.2 and encodes the FLT3 protein (15). Human FLT3 protein is mainly composed of an extracellular domain from N-terminal to C-terminal, a transmembrane domain, an intracellular juxta membrane domain (JMD) and two TKD domains. In the normal human body, the FLT3 protein is in an active protein-inhibited monomer state. When it binds to the N terminus of the FLT3 ligand (FL) at the interaction site of the FLT3 extracellular domain, FLT3 self-dimerizes, then forms an activated state and triggers the phosphorylation cascade of downstream target proteins, affecting the proliferation and differentiation of hematopoietic cells. It plays an important role in maintaining the homeostasis of the hematopoietic system (16). At present, FLT3 has become a therapeutic target of great application value, and there are more than ten small molecule inhibitors in clinical trials or approved, and they have achieved different degrees of clinical efficacy (17).

Therefore, a meta-analysis of such studies was conducted to provide reliable evidence-based medical evidence for clinical practice. Meta-analysis is to summarize the results of multiple studies with the same research purpose and analyze and evaluate the combined effect size. This article mainly included retrospective and prospective case-control studies and analyzed them, to better evaluate and analyze the relationship between them from the perspective of evidence-based medicine, and guide clinicians to make more reasonable and correct decisions.

Materials and Methods

Literature search

English databases such as Pubmed were searched from the establishment of the database to April 2023. The search term was set as "FLT3 inhibitor". "Allogeneic hematopoietic stem cell transplantation"; "malignant hematologic disease", "chronic graft-versus-host disease". The above phrases were optimally combined and searched to obtain the maximum number of relevant literatures. The search terms appeared in titles, keywords, abstracts, etc. Some references to the included literatures could be traced, and the full texts were manually retrieved and included.

Literature inclusion and exclusion criteria

Inclusion criteria

The published literature on FLT3 inhibitors in MHD with allo-HSCT was limited to English, and there was no publication time limit. The experimental group was treated with an FLT3 inhibitor, and the controls were treated without an FLT3 inhibitor. The original data of patients after treatment (RFS, OS, and cGVHD) were available.

Exclusion criteria

Literaturewithout complete data; Duplicate published literature; When two studies from the same institution reported the same objective outcome, better quality reports were included; Review or commentary; Animal or cell experiments.

Quality evaluation of literature

Two researchers independently reviewed the literature by reading the full text and extracting relevant data. Any discrepancies were resolved through discussion or with the help of a third researcher. The Jadad scale was employed to assess the quality of the literature. This assessment considered whether it was a randomized controlled trial, whether the randomized method was appropriate, whether it was a double-blind test, whether the double-blind method was appropriate, and whether patients were lost to follow-up or withdrew during the literature research, with explanations provided and whether it adopted the intention-to-treat analysis method. Each "Yes" response earned 1 point, and "No" received 0, with a total score of 5. Studies scoring less than 2 were considered low-level, while studies with scores above 2 were deemed high-level.

The Cochrane Reviewer's Handbook version 4.2.5 was employed to evaluate the studies' quality. The evaluation considered whether it was randomized, there was allocation concealment, a blinded trial was adopted, the data were complete, there was selective reporting of results, and there were other biases.

Data extraction

To screen the literature, two researchers independently assessed whether each study was a case-control or cohort study. All studies that met the requirements for meta-analysis were incorporated, evaluating their quality. Studies with repeated reports, poor quality, or insufficient information were excluded. Data were extracted into established tables, creating and checking a database. In case of incomplete reports, the authors were contacted to determine the exclusion of articles that were not available. Data extraction was performed only after obtaining the full text of the study, and if there were duplicate reports, the most recent study was selected. The data extracted included basic information on the literature, such as the title, first author, and publication year, as well as basic characteristics of the subjects (sample size and baseline comparability). Research methods, study design, intervention measures of two groups, evaluation indicators, and outcome data were also extracted.

Statistical analysis

It adopted the Revman5.3 software provided by the Cochrane Collaboration. The results were tested for heterogeneity at a significance level of $\alpha=0.05$ using the Peto method. If $I^2<50\%$, the literature was considered homogeneous, and the fixed effect model was adopted. If $I^2>50\%$, the literature was considered heterogeneous, and the random effect model was adopted. Results with the same measurement unit were expressed as weighted mean difference (WMD), while those with different units were expressed as standard deviation (SD). Count data were expressed as relative risk (RR), and all results were presented with a 95% CI. To evaluate publication bias, it drew a funnel plot and assessed the symmetry and concentration of the literature toward the midline. It also performed a sensitivity analysis to evaluate whether the results were reliable and stable.

Results

Literature searching and overview analysis

3,349 relevant articles were searched, including 1,137 articles retrieved from the Medline database, 1,100 articles retrieved from EMbase, 68 articles retrieved from the EBSCO database, and 1,044 articles retrieved manually. According to the inclusion and exclusion criteria, 1,400 ar-

Table 1. Basic data of the literatures.

References	Research Group	Controls	Research group treatment methods	Controls treatment methods	Indicators
Burchertet al. (18)	43	40	Sorafenib	Placebo	RFS, OS, and cGVHD
Brunner et al. (19)	26	55	Sorafenib	Placebo	RFS, OS, and cGVHD
Maziarz et al. (20)	30	30	Standard-of-care (SOC) + midostaurin	SOC	RFS, cGVHD
Sasaki et al. (21)	79	104	Sorafenib plus intensive therapy	Intensive therapy	OS
Nanno et al. (22)	9	25	Ponatinib	No ponatinib	RFS, OS, and cGVHD
Xuan et al. (23)	100	102	Sorafenib maintenance therapy	Non-maintenance treatment	OS and cGVHD
Aydin et al. (24)	21	22	Sorafenib	No sorafenib	OS
Xu et al. (25)	100	102	Sorafenib maintenance therapy	Non-maintenance treatment	OS and cGVHD
Xuan et al. (26)	26	50	Sorafenib	No sorafenib	OS

ticles not meeting the requirements were excluded. By reading titles and abstracts, 1,575 articles that obviously did not meet the inclusion criteria were excluded. By reading the full text, 362 articles were excluded. Through careful reading, 3 literatures were excluded, and 9 literatures were finally included (18-26). The detailed screening situation is illustrated in Figure 1. The basic data of patients and research indicators in the literatures are given in Table 1.

Assessment of bias risk

Firstly, the bias risk assessment tool recommended by the Cochrane Handbook of Systematic Reviews was adopted to evaluate the quality of the included literatures (Figures 2 and 3). There was no random sequence generation, incomplete outcome data, and selective reporting in these 9 studies. In addition, the overall risk was low.

RFS of patients following treatment

Four articles were included in the analysis of the RFS (Figure 4). The heterogeneity analysis presented that I^2=0%, P=0.64, indicating homogeneity. The comprehensive model analysis revealed an odds ratio of 3.28 with a 95% CI of 1.76-6.11, Z=3.75, P=0.0002. The RFS of patients treated with FLT3 inhibitor was different from that of patients without FLT3 inhibitor (P<0.05). Figure 5 presents the funnel plot of the analysis of RFS following treatment, which is generally symmetric. Most data points fall within the 95% CI, indicating that publication bias was minimal.

OS of patients after treatment

The results of the meta-analysis of eight articles analyzing the OS following treatment indicated a statistically significant difference in OS between patients with FLT3 inhibitor and those without FLT3 inhibitor, with an odds ratio of 2.85 and a 95% CI of 2.12-3.83, Z=6.95, P<0.00001. The heterogeneity analysis suggested that there was no obvious heterogeneity. The funnel plot for the analysis of OS revealed a symmetrical distribution. These findings suggest that FLT3 inhibitors may improve OS in patients with certain conditions, providing support for the

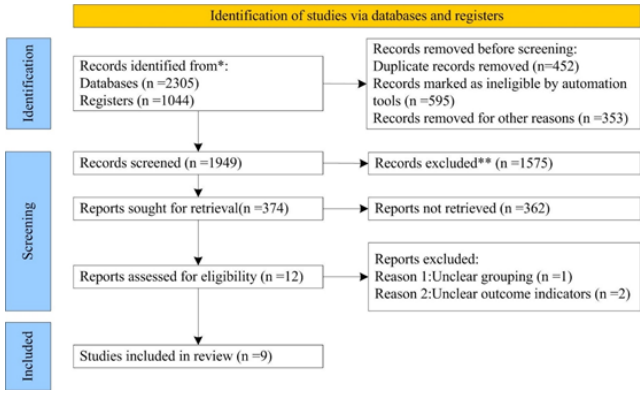

Figure 1. Retrieval flow chart.

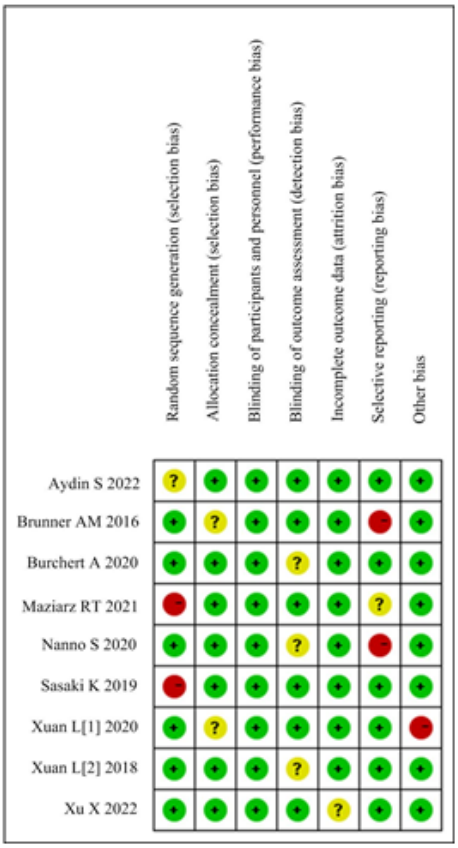

Figure 2. Risk of bias assessment.

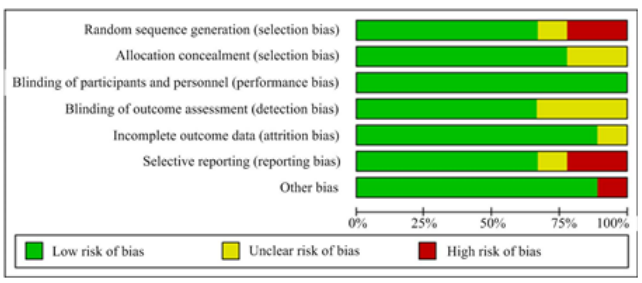

Figure 3. Bar chart of bias risk assessment.

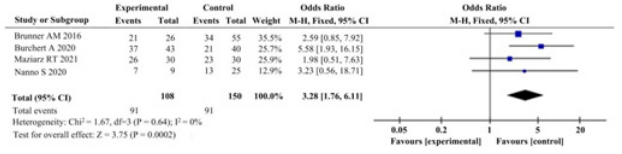

Figure 4. Forest plot of RFS of patients after treatment.

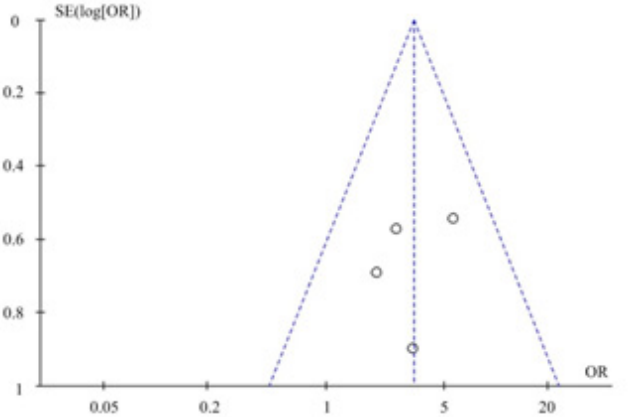

Figure 5. Funnel plot of RFS.

use of FLT3 inhibitors (Figures 6 and 7).

Occurrence of cGVHD following treatment

Heterogeneity analysis in six articles to analyze the occurrence of cGVHD after treatment revealed that I^2=84%, P<0.00001, so the random effects model was applied for the subsequent exploration (Figure 8). The results of the comprehensive model analysis presented that odds ratio=1.06, 95% CI = 0.37-2.98, Z=0.11, P=0.92. It seems that there was a similar incidence of cGVHD between patients with FLT3 inhibitors and those without FLT3 inhibitors(P>0.05). The funnel plot of the analysis of cGVHD occurrence in patients was essentially symmetric (Figure 9).

Discussion

Allo-HSCT is an effective treatment for MHD. The main source of hematopoietic stem cells is HLA-matched sibling donors, but the probability of finding an HLA-matched sibling is low. With the development of transplantation technology, haploidentical HSCT has been increasingly adopted in clinical practice. It provides a safe and effective alternative donor for patients who do not have an identical sibling donor (27). Selection of transplants with an incomplete HLA match may increase the risk of GVHD due to alloimmune responses that may be caused by HLA gene products. FLT3 gene mutation is found in about 30% of patients with acute myeloid leukemia (AML), especially FLT3-ITD mutation, which is not only a high incidence, but also a high-risk factor affecting the prognosis of the disease. Both NCCN and European Hematology guidelines classified it as the high-risk group affecting the prognosis (28). Therefore, FLT3 has become a promising therapeutic target, which has attracted extensive attention. If a breakthrough is made in the targeted therapy of this gene, the prognosis of AML patients will be greatly improved. It aimed to explore the application outcome of FLT3 inhibitors in MHD with allo-HSCT.

The results revealed that the RFS and OS of patients

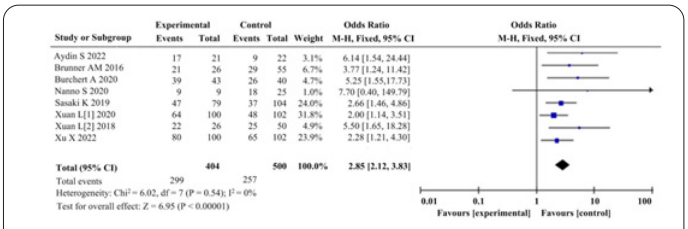

Figure 6. Forest plot of OS analysis following treatment.

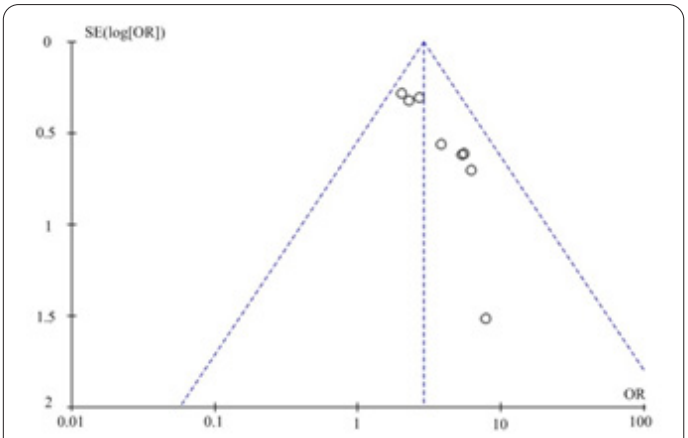

Figure 7. Funnel plot of OS.

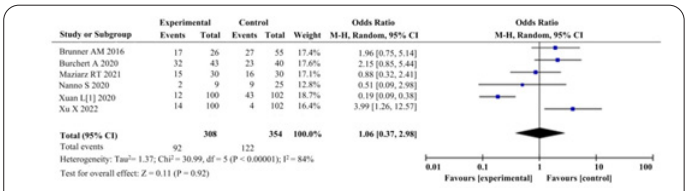

Figure 8. Analysis of forest plot of the occurrence of cGVHD after treatment.

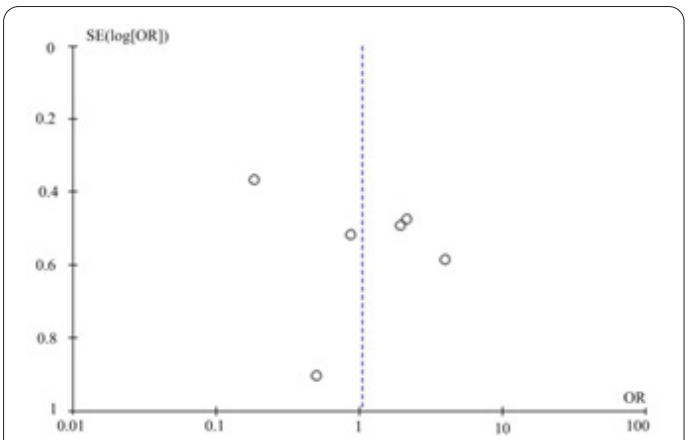

Figure 9. Funnel plot for cGVHD occurrence.

treated with FLT3 inhibitor were improved as against patients without FLT3 inhibitor (P<0.05), but they were similar in the occurrence of cGVHD(P>0.05). Although allo-HSCT can achieve long-term disease-free survival for MHD patients, the overall efficacy is poor and the survival rate after relapse is low. The results indicate that FLT3 inhibitor can effectively reduce the relapse rate of MHD patients and improve the therapeutic outcome, and does not affect the occurrence of cGVHD following treatment. Majothi et al.(29) evaluated the application effect of five different FLT3 inhibitors (sorafenib, leseltinib, midotrine, gefitinib, and quizartinib) in AML and presented that FLT3 inhibitors could effectively improve the treatment outcome and increase the survival rate of patients. However, more

data are needed to support the adverse events. Bewersdorf et al. (30) conducted a meta-analysis of hypomethylating agents and FLT3 inhibitors as maintenance therapy for AML and myelodysplastic syndrome after allo-HSCT, and the results showed that hypomethylating agents and FLT3 inhibitors could prolong and improve OS and RFS, with good safety; Domestic studies have also conducted a meta-analysis of FLT3 inhibitors as maintenance therapy for AML patients with FLT3 mutation after allo-HSCT. The maintenance of FLT3 after transplantation can improve the survival rate and reduce the recurrence of AML patients with FLT3 mutation, and it is tolerable (31). These results were consistent with the results of this article.

Conclusion

The meta-analysis showed that FLT3 inhibitors could effectively increase the RFS and OS of patients with MHD receiving allo-HSCT, improve the treatment effect, and not affect the occurrence of cGVHD following treatment, which has application value. Due to the incomplete data and small number of patients, most of the included literatures were the application of FLT3 inhibitor sorafenib in the treatment of MHD with allo-HSCT, and other drugs were few. Therefore, the results have certain limitations and need to be further improved in the future. The application effect of FLT3 inhibitor in the treatment of MHD with allo-HSCT will be comprehensively analyzed by more clinical data.

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