Meta-analysis of decitabine pretreatment-based allogeneic hematopoietic stem cell transplantation affecting transplantation-related complications and prognosis in patients with malignant hematological disease

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ABSTRACT

Malignant hematological diseases (MHD) are a kind of bone marrow hematopoietic system disease caused by malignant clonal proliferation, including leukemia, lymphoma, myelodysplastic syndrome, etc. At present, there are too few meta-analyses on the effect of decitabine pretreatment-based allogeneic hematopoietic stem cell transplantation (allo-HSCT) on transplantation-related complications and prognosis of MHD patients. A systematic search of PubMed, MEDLINE, Science Direct, The Cochrane Library, CNKI, and CBM was performed. The relevant literature on decitabine pretreated allo-HSCT for the treatment of MHD was screened, and the screening time was up to May 1, 2023. After extensive investigation, only 5 articles met the criteria. Result: The results of this article showed that the odds ratio of mortality after decitabine conditioning treatment was 2.35, the incidence of complications after transplantation was 1.07, and the survival rate following transplantation was 0.82. Decitabine-based conditioning regimen can reduce the incidence of transplantation-related complications and improve the prognosis of MHD patients receiving allo-HSCT. Although it has limitations, it still has very important clinical implications.

Introduction

Malignant hematological diseases (MHD) are cancerous diseases resulting from abnormalities in the development of white blood cells or lymphocytes (1). The disease has a lot of different kinds, the most common are acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), Hodgkin’s lymphoma, and non-Hodgkin’s lymphoma, etc. The etiology of MHD is not fully understood, but certain factors, such as genetic mutations, environmental factors, infection, and disease treatment, may cause it to occur. The symptoms of MHD vary according to its type, but most types can cause discomfort symptoms such as fatigue, fever, lymphadenopathy, anemia, easy bleeding/congestion, and pain (2). The treatment of MHD usually includes chemotherapy, radiotherapy, stem cell transplantation, and immunotherapy. The treatment plan is usually based on the specific condition of the patient, such as the type of lesion, age, and physical health. Stem cell transplantation is one of the most effective treatments for MHD at present, which can be used to replace abnormal blood cells in MHD patients (3).

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a treatment for blood-related diseases such as MHD by transplanting hematopoietic stem cells from another person into the patient’s body, to replace the original and abnormal hematopoietic system (4). Typically, this approach employs bone marrow, peripheral blood, or cord blood as the source of hematopoietic stem cells. allo-HSCT is the opposite of autologous-HSCT (transplantation of stem cells from the same patient) (5). Allo-HSCT may allow for a wider selection of stem cell donors, as first-degree relatives may not be suitable candidates for hematopoietic stem cell donation. However, allo-HSCT also faces a higher risk of graft rejection. allo-HSCT usually requires the use of immunosuppressive agents to help the patient’s body accept the recipient’s transplanted foreign stem cells. Prior to surgery, patients are treated with systemic chemotherapy or radiation to destroy the patient’s native hematopoietic stem cells to create space for allogeneic stem cell transplantation. However, this treatment option also faces certain risks, including infection, post-transplant complications, and long-term genetic problems (6).

Decitabine is a new type of anti-tumor drug, which achieves an anti-cancer effect by inhibiting DNA synthesis and cell division (7). Decitabine is commonly used in the treatment of breast cancer, prostate cancer, non-small cell lung cancer and other malignant tumors. In recent years, the application of decitabine in the conditioning of HSCT has received extensive attention (8). Decitabine pretreatment can reduce the incidence of graft-versus-host disease (GVHD) by eliminating the abnormal hematopoietic system of patients, and it can enhance the anti-tumor effect of grafts and improve the survival rate of patients (9). Howe-
ver, decitabine has strong toxic and side effects, and the effect of decitabine conditioning on transplantation-related complications and prognosis is still controversial (10).

This article aimed to explore the effect of decitabine conditioning-based allo-HSCT on transplantation-related complications and prognosis of MHD patients through meta-analysis, to provide more accurate treatment strategies and guidance for clinical practice.

Materials and Methods

Literature search

This article searched PubMed, Embase, Cochrane Library, and CNKI databases until April 2023. Chinese search terms included: decitabine, allogeneic hematopoietic stem cell transplantation, allo-HSCT, malignant hematologic disease, graft-versus-host disease, and decitabine. The identification of the search strategy was done through multiple pre-searches, manually searching professional journals to avoid missing relevant literature. In addition, the subjects of the retrieved studies were all human. The search process used a combination of subject headings and free words to conduct multiple searches to obtain relevant literature that can be included in the reference list, and then the search engine was adopted to further trace these literatures.

Literature inclusion and exclusion criteria

The PICOS design framework was adopted to select suitable randomized controlled trials (RCTs) for inclusion, which were screened according to prespecified eligibility criteria. Participants, interventions, control groups, outcomes, and study design were considered in this framework. With such a framework, it can more systematically select suitable RCTs for inclusion and improve the reliability and comparability of studies. The inclusion and exclusion criteria of the literature are shown in Tables 1 and 2.

It was independently completed by two experienced researchers. First, they would select the required articles through the title and content of the references. Then, they would read the full text of the eligible articles according to the pre-set criteria and select the articles that met the requirements. They extracted relevant information from the articles, including first author, year of publication, subject characteristics, comparator medications, duration of follow-up, and clinical-research-related outcome measures (e.g., mortality, hospitalization risk, and changes in measures of cardiac function). In cases of doubt or controversy, they consulted with a third investigator and made the final decision.

Data extraction

In modern scientific research, literature screening and data extraction are very important links. The quality of these links directly affects the reliability and accuracy of the research results. Therefore, in order to ensure the scientific validity and credibility of the study, researchers need to adopt a rigorous method for literature screening and data extraction. In this process, the use of tools such as Microsoft Excel (Microsoft, the United States) can greatly improve the efficiency of researchers. When conducting literature screening and data extraction, researchers need to follow certain standards and norms. These standards and norms usually include inclusion and exclusion criteria. Inclusion criteria refer to literature or data that meet the objectives and questions of the study, whereas exclusion criteria refer to literature or data that do not. By strictly following these criteria and norms, researchers can guarantee that the screened and extracted data have a certain degree of reliability and accuracy. Disagreements can be resolved through mutual consultation. For example, a consensus can be reached by discussing, comparing, and analyzing different literature or data to find out the differences and commonalities. In this way, researchers can guarantee higher reliability and accuracy of the screened and extracted data. The extracted data information is illustrated in Table 3.

Literature evaluation criteria

Revman5.3 software was employed to evaluate the included literatures using the RCT bias risk assessment method recommended by the Cochrane Handbook for

<p>| Table 1. Inclusion criteria for literature. |</p>
<table>
<thead>
<tr>
<th>Serial number</th>
<th>Specific requirements</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Patients with MHD such as leukemia, lymphoma, and myelodysplastic syndrome</td>
</tr>
<tr>
<td>2</td>
<td>Decitabine-based conditioning regimen for stem cell transplantation</td>
</tr>
<tr>
<td>3</td>
<td>The incidence of transplantation-related complications, the survival rate after transplantation, and overall survival (OS)</td>
</tr>
<tr>
<td>4</td>
<td>Clinical RCTs, cohort studies, case-control studies, etc.</td>
</tr>
</tbody>
</table>

<p>| Table 2. Exclusion criteria. |</p>
<table>
<thead>
<tr>
<th>Serial number</th>
<th>Specific requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The study sample size was less than 20 patients; Too small a sample may lead to bias and insufficient power</td>
</tr>
<tr>
<td>2</td>
<td>The subjects were patients with other medical conditions</td>
</tr>
<tr>
<td>3</td>
<td>Study of non-decitabine pretreatment regimens</td>
</tr>
<tr>
<td>4</td>
<td>The data were incomplete, the results were not clear, the sample size was too small to be analyzed</td>
</tr>
<tr>
<td>5</td>
<td>The types of literature were case reports, comments, expert opinions, and other invalid literatures and non-clinical research</td>
</tr>
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mortality after decitabine pretreatment-based allo-HSCT was 2.35, 95%CI (0.99, 5.63), I^2=0, P=0.894. The OR value revealed that the mortality of patients post-treatment in each experimental group was obviously different. The lowest OR was 1.30, 95%CI (0.18, 9.74), and the highest OR was 3.03, 95%CI (0.32, 28.81) (Figure 4).

Figure 5 shows a funnel plot of patient mortality with small risk of bias across studies. In conclusion, decitabine conditioning-based allo-HSCT has a mortality reduction effect in the treatment of MHD.

Meta-analysis of complications post-transplantation

Figure 6 presents that the OR value of complications was 1.07, 95%CI (0.68, 1.68), I^2=0.02%, P=0.735. The OR value indicated that there was a low difference in the probability of complications among the groups post-treatment. The lowest OR value was 0.73, 95%CI (0.26, 2.05), and the highest OR value was 1.78, 95%CI (0.69, 4.58).

Results

Search results and basic information on literature

328 articles were retrieved, including 78 duplicate articles, 83 unqualified articles, and 35 articles with other problems. 132 articles were selected. 43 articles were excluded by reading the abstract and title, 61 articles with incorrect research types, 13 articles with unclear treatment results, 6 articles with unclear results, and 4 articles with animal experiments were excluded by reading the content of the articles. A total of 5 studies were included. The flow chart is illustrated in Figure 1.

Among the included 5 articles, each mentioned the mortality, complications, and survival rate of the patients, among which the basic characteristics of the patients are given in Table 5.

Risk of bias assessment

After quality evaluation, there were 4 articles with an evaluation grade of A, accounting for 80%, and 1 article with an evaluation grade of B, accounting for 20%. The evaluation chart and summary chart of the risk deviation of references were drawn by RevMan5.3 software (Figures 2 and 3).

Meta-analysis of mortality

Mortality as a clinical outcome index, the OR value of...
Figure 7 suggests the small risk of bias in each study. Therefore, decitabine conditioning-based allo-HSCT did not obviously reduce the incidence of complications in MHD.

Meta-analysis of post-transplant survival

Figure 8 presents that the OR value of survival rate was 0.82, 95%CI (0.54, 1.23), $I^2=0\%$, $P=0.849$, indicating that there was a low difference in survival rate among the groups post-treatment. The lowest OR value was 0.61, 95%CI (0.18, 1.44), and the highest OR value was 1.00,
patients before allo-HSCT, in order to improve the success rate of transplantation and reduce the risk of complications after transplantation (19). Conditioning includes chemotherapy, radiotherapy, immunosuppressants, and other treatment methods, aiming to eliminate malignant cells such as leukemia or lymphoma in the patient’s body while inhibiting the patient’s immune system and reducing the rejection of allogeneic hematopoietic stem cells (20). Conditioning can also promote the proliferation and spread of hematopoietic stem cells and improve the recovery rate of hematopoietic function post-transplantation (21,22).

Decitabine can inhibit cell proliferation by preventing purine nucleotide synthesis during DNA synthesis (23,24). In transplantation conditioning, decitabine reduces the incidence of graft rejection by regulating the host immune system (25). In addition, decitabine can also enhance the anti-tumor effect after transplantation by inducing immune tolerance and activating tumor-specific T cells (26). The action of these mechanisms can not only prevent the occurrence of complications at an earlier time but also enhance the transplant survival rate post-transplantation (27).

However, this article has some limitations. Due to the uneven geographical distribution of the included literature, and the interference factors in some studies can't be completely controlled, some heterogeneity still exists, which will have an impact on the meta-analysis. Secondly, although only high-quality studies were included, there are still some shortcomings that need to be paid attention to. For example, the sample sizes of the included studies were small, and some data quality may have been compromised by several factors, including sample size, flaws in

95%CI (0.49, 2.02).

Figure 9 illustrates that decitabine pretreated allo-HSCT can improve the survival rate in MHD.

Reliability analysis

According to the results of the meta-analysis, no significant changes were found even when different analysis models were applied to summarize the results. This indicated that the included literatures had good stability. In addition, the consistency of the validation can also be demonstrated by using models such as funnel asymmetric linear regression for analysis.

Discussion

This meta-analysis demonstrated that a decitabine conditioning regimen could clearly reduce the incidence of transplantation-related complications, including acute and chronic GVHD, and significantly improve the prognosis of MHD patients after allo-HSCT, including post-transplantation survival rate and OS. This conclusion is consistent with the results of previous studies, indicating that the decitabine conditioning-based regimen is a safe and effective treatment for MHD patients.

Different from autologous-HSCT, allo-HSCT uses human leukocyte antigen (HLA) differences between donors and recipients, so adequate immunosuppressive therapy is required to avoid graft rejection and GVHD (17). The success rate of allo-HSCT is low, but for some patients, it is the only treatment option (18). allo-HSCT conditioning refers to a series of treatments and preparations for
study design, and the risk of selective reporting. Because decitabine has been used in combination with other agents in some studies, the effect of this multimodal treatment needs to be further evaluated in future studies. Since there is little literature on the use of decitabine alone for conditioning of HSCT, there is more literature on the use of decitabine plus other drugs, and some literature has patients treated with only one treatment modality and no control group exists. Therefore, only 5 studies met the inclusion requirements after careful screening.

The analysis and evaluation of allo-HSCT based on a decitabine conditioning regimen can provide clinicians with more accurate treatment plans and improve the survival rate of patients after transplantation. This article provides some enlightenment for future research directions, such as conducting studies in a wider range to evaluate the effect of decitabine when used in combination with other drugs.

In conclusion, decitabine conditioning-based allo-HSCT can reduce the mortality of MHD patients, improve the survival rate, and improve the prognostic indicators, but it has little effect on postoperative complications. Although it has limitations, it still has very important clinical significance. More rigorous studies are needed to ensure the safety and efficacy of this treatment and to provide a better plan for the clinical treatment of MHD.

Conclusion
Decitabine conditioning-based allo-HSCT can reduce the incidence of transplantation-related complications, including aGVHD and cGVHD, in MHD patients. In addition, decitabine conditioning significantly improved the survival rate of patients after allo-HSCT. This conclusion suggests that decitabine conditioning is a safe and effective treatment for MHD. Although further evidence is needed, this method has become one of the important strategies in clinical practice.

References


