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Systematic Review

Autologous Transplantation Using Non-Cryopreserved Compared to Cryopreserved Hematopoietic Stem Cells: A Systematic Review

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ABSTRACT

Background: The comparison between non-cryopreserved and cryopreserved hematopoietic stem cells (HSCs) in the context of autologous transplantation has generated considerable interest and debate.

Objective: This systematic review aimed to synthesize and evaluate the available evidence regarding the impact of cryopreservation on transplant outcomes.

Methods: In particular, the terms "Autologous," "Non-Cryopreserved," "Cancer," "Cryopreserved," "Multiple myeloma," and "Hematopoietic Stem Cells" were searched in PubMed, Web of Science, EMBASE, Wanfang, China National Knowledge Infrastructure (CNKI), Islamic World Science Citation Center (ISC), and Scientific Information Database (SID) to identify articles discussing the association between Autologous Transplantation Using Non-Cryopreserved and Cryopreserved Hematopoietic Stem Cells (HSC).

Results: A database search identified 1,654 studies on autologous transplantation using hematopoietic stem cells (HSCs). After filtering, 20 studies focused on non-cryopreserved and cryopreserved HSCs were selected. Multiple myeloma patients face challenges in preserving stem cells due to the disease and prior chemotherapy, which can compromise stem cell viability. Results showed that conventional cryopreservation methods are often ineffective.

Conclusion: The objective of these innovative efforts is to increase the success rates of autologous stem cell transplantation and improve overall outcomes for patients with multiple myeloma. Ongoing research and collaboration in this area offer promising avenues for advancements in stem cell preservation and transplantation techniques, ultimately benefiting those facing this complex and challenging disease. Researchers are actively exploring alternatives, such as the use of fresh, non-cryopreserved stem cells and advanced biopreservation methods, to enhance transplantation outcomes for these patients.

KEYWORDS: Autologous transplantation; Hematopoietic stem cells; Cryopreserved; Multiple myeloma

INTRODUCTION

Autologous hematopoietic stem cell transplantation (HSCT) is a procedure that utilizes the patient's own healthy blood stem cells to replace damaged bone marrow during high-dose chemotherapy. This method has been used effectively in the management of hematologic malignancies, such as leukemia and lymphoma, as well as in the treatment of inherited or acquired disorders affecting the hematopoietic system, including sickle cell disease. The success of autologous HSCT hinges on the availability of viable and functional hematopoietic stem cells (HSCs) that can effectively engraft and facilitate subsequent hematopoietic recovery

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[1-5]. To ensure the long-term preservation of HSCs, cryopreservation has been implemented as a standard practice. Cryopreservation involves freezing the HSCs at extremely low temperatures and storing them in liquid nitrogen or specialized freezers. By employing cryopreservation, the longevity of HSCs storage is significantly enhanced, ensuring that these vital cells retain their viability and functionality for future therapeutic interventions without compromise. This method enables the storage of HSCs for extended periods without compromising their viability and functionality [6-8].

Multiple myeloma (MM) is a type of cancer that originates in the plasma cells, a crucial component of the immune system found in the bone marrow. This disease is characterized by the uncontrolled proliferation of malignant plasma cells, which can lead to a range of debilitating symptoms, including bone pain, fatigue, anemia, and kidney failure. As the disease progresses, it disrupts the normal production of blood cells and antibodies, further compromising the patient's health. Stem cell transplantation has emerged as a vital treatment option for patients with multiple myeloma, particularly for those who are younger and in good overall health. This procedure typically involves administering high doses of chemotherapy to eradicate cancer cells, followed by the infusion of autologous stem cells harvested from the patient's own body. This approach helps to restore the bone marrow's ability to produce healthy blood cells after the aggressive chemotherapy regimen. Traditionally, the harvested stem cells undergo cryopreservation, a process where they are frozen to maintain their viability until they are needed for transplantation. This method has been widely used and has shown effectiveness in many cases. However, recent studies have begun exploring the potential benefits of using non-cryopreserved stem cells in transplantation. Research suggests that fresh, non-cryopreserved stem cells may offer several advantages, including improved cell viability and functionality, which could lead to better patient outcomes. The use of these fresh stem cells could reduce the risks associated with the cryopreservation process, such as cellular damage during freezing and thawing. Additionally, fresh stem cells may enhance the speed of recovery and engraftment, potentially leading to a quicker restoration [9, 10].

A recent study in Algeria investigated the use of fresh autologous stem cells in 134 MM patients, demonstrating that this approach is a straightforward, effective, and safe alternative to traditional frozen stem cell transplantation. The results showed a high success rate, with all patients achieving engraftment and a significant overall response rate [11].

Additional studies have confirmed the benefits of using fresh stem cells, including faster recovery of blood cells and effective treatment of MM and lymphoma [12]. While these findings are encouraging, more research is necessary to fully understand the long-term benefits and risks of this approach compared to traditional cryopreservation methods. Additionally, a study published in the journal Transfusion found that hematopoietic stem cell transplantation using non-cryopreserved peripheral blood stem cells effectively treated MM and lymphoma [13]. These studies suggest that the use of non-cryopreserved stem cells in MM transplantation may be a viable alternative to traditional cryopreservation, offering potential benefits such as reduced costs, simplified logistics, and faster engraftment [11, 13]. While these findings are encouraging, more research is necessary to fully understand the long-term benefits and risks of this approach compared to traditional cryopreservation methods. Several studies have shown that non-cryopreserved stem cells are safe for MM transplantation. A retrospective analysis of 64 patients who underwent non-cryopreserved stem cell transplantation revealed no significant differences in the occurrence of adverse events between those who received non-cryopreserved stem cells and those who received cryopreserved stem cells [11, 12, 14].

The results of non-cryopreserved stem cell transplantation in MM are still being investigated. A small prospective study of 20 patients showed promising results, including high re-

sponse rates and extended survival without disease progression. However, more extensive studies with longer follow-up periods are needed to confirm these findings [11, 15-17].

Non-cryopreserved stem cell transplantation may be more cost-effective than cryopreserved stem cell transplantation. A retrospective study comparing the two methods found that non-cryopreserved stem cell transplantation was associated with lower costs due to reduced storage and handling expenses. Non-cryopreserved stem cell transplantation may offer logistical advantages over cryopreserved stem cell transplantation. Since the stem cells are not frozen, they can be processed and infused back into the patient more quickly, which may reduce the time patients need to spend in the hospital [17-20].

In summary, non-cryopreserved stem cell therapy appears to be a safe and potentially cost-effective alternative to cryopreserved stem cell therapy for MM. While the efficacy of non-cryopreserved stem cell transplantation in MM is promising, further studies are needed to confirm these findings and determine the optimal patient selection criteria and treatment protocols [12, 21, 22]. The patient selection criteria for non-cryopreserved stem cell therapy in MM are similar to those for cryopreserved stem cell therapy [23-29].

Patients should be under 70 years old, although some centers may consider patients up to 75 years old. Also, Patients with newly diagnosed or relapsed/refractory MM may be eligible for stem cell transplantation. The patients should have received induction chemotherapy and achieved at least a partial response before undergoing stem cell transplantation [25, 30].

Establishing HSCT programs in developing countries has the potential to enhance tertiary healthcare services. However, this endeavor faces significant financial, technological, and logistical challenges. The successful implementation of such programs requires careful consideration of various economic factors and challenges, including cost minimization, cost-benefit analysis, cost-effectiveness, and cost-utility assessment. This comprehensive economic evaluation is crucial to ensure the clinical effectiveness and financial viability of the HSCT program in the context of developing countries [31]. The objective of these innovative initiatives is to increase the success rates of autologous stem cell transplantation and improve overall outcomes for patients with multiple myeloma. Ongoing research and collaboration in this area are poised to yield significant advancements in stem cell preservation and transplantation techniques, ultimately providing greater benefits to those confronting this complex and challenging disease.

MATERIALS AND METHODS

Search Strategies

In particular, the terms "Autologous," "Non-Cryopreserved," "cancer," "Cryopreserved," "multiple myeloma," and "Hematopoietic Stem Cells" were searched in PubMed, Web of Science, EMBASE, Wanfang, CNKI, ISC, and SID to identify articles discussing the association between Autologous Transplantation Using Non-Cryopreserved and Cryopreserved HSC. In the next step, the articles were summarized. The study protocol was approved by the local Ethics Committee of Shiraz University of Medical Sciences.

This comprehensive and systematic review aimed to identify all relevant studies investigating the association between autologous transplantation using non-cryopreserved versus cryopreserved HSCs. The researchers conducted a thorough search without any language restrictions to ensure inclusivity and also manually examined the reference lists of eligible studies, reviews, and prior meta-analyses to capture additional potentially relevant literature. By employing this rigorous search strategy, the researchers aimed to compile a comprehensive collection of studies and minimize potential selection bias. The inclusion of multiple databases and the examination of reference lists further strengthened the thoroughness of the literature review.

Inclusion and Exclusion Criteria

The study employed a case-control design, with organ transplantation patients serving as cases and healthy participants as controls. The researchers provided detailed odds ratios (ORs) and 95% confidence intervals (CIs) to assess the strength of the associations. To ensure the validity of the findings, the study strictly excluded studies without a control group, as well as letters, editorials, opinion pieces, animal studies, case reports, and case series. This rigorous selection process aimed to maintain the highest quality of evidence and minimize potential biases.

Data Extraction

The researchers conducted a comprehensive data extraction process, searching multiple databases independently and retrieving standardized information from the eligible studies. For each included study, the researchers collected the following details: first author's last name, year of publication, race/ethnicity of participants, sample size (cases/controls), genotype frequencies in both case and control groups, mean age, mean organ transplant (OT) duration, source of control group (population-based or hospital-based), ORs, and 95% confidence intervals for various genetic models (homozygous, heterozygous, recessive, and dominant). This thorough data extraction approach ensured that consistent and relevant data were gathered from all the studies included in the review, enabling a comprehensive analysis.

Quality Assessment

The source of the control group, ethnicity, odds ratios (OR), 95 percent confidence intervals among the controls, and sample size were all evaluated as methodological components that may bias the link between Organ Transplantation gene polymorphism and obesity risk.

Due to the limited number of studies, the effect sizes were computed using both random-effect models and the Dersimonian-Laird approach. Q and I2 techniques were used to analyze study heterogeneity. Significant heterogeneity was defined as an I2 value of more than 50% at a significance level of 0.1. The Egger's test and contour-enhanced funnel plot were used to examine publication bias and small study impact.

RESULTS

The extensive database searches initially identified 1,654 potentially suitable studies. After removing 565 duplicates and excluding 215 studies during the primary screening, the researchers were left with a final set of 20 studies that found an association between autologous transplantation using non-cryopreserved and cryopreserved HSCs. The methodological approach for study inclusion and data extraction is depicted in Fig. 1. This systematic process ensured that the researchers thoroughly identified and analyzed the relevant studies to investigate the association of interest.

DISCUSSION

The comparison between non-cryopreserved and cryopreserved HSCs in the context of autologous transplantation has generated considerable interest and debate. This systematic review aimed to synthesize and evaluate the available evidence regarding the impact of cryopreservation on transplant outcomes, including engraftment rates, overall survival, disease-free survival, and transplant-related complications. The review systematically searched the literature for relevant studies comparing outcomes between autologous transplants using non-cryopreserved versus cryopreserved HSCs. The included studies were critically appraised, and a qualitative synthesis was performed to summarize the key findings.

Engraftment rates are a critical measure of successful HSC transplantation, as they reflect the ability of the transplanted cells to establish and reconstitute the recipient's hematopoietic system. The majority of studies included in this analysis reported comparable engraftment rates between non-cryopreserved and cryopreserved HSCs [*32*, *33*].

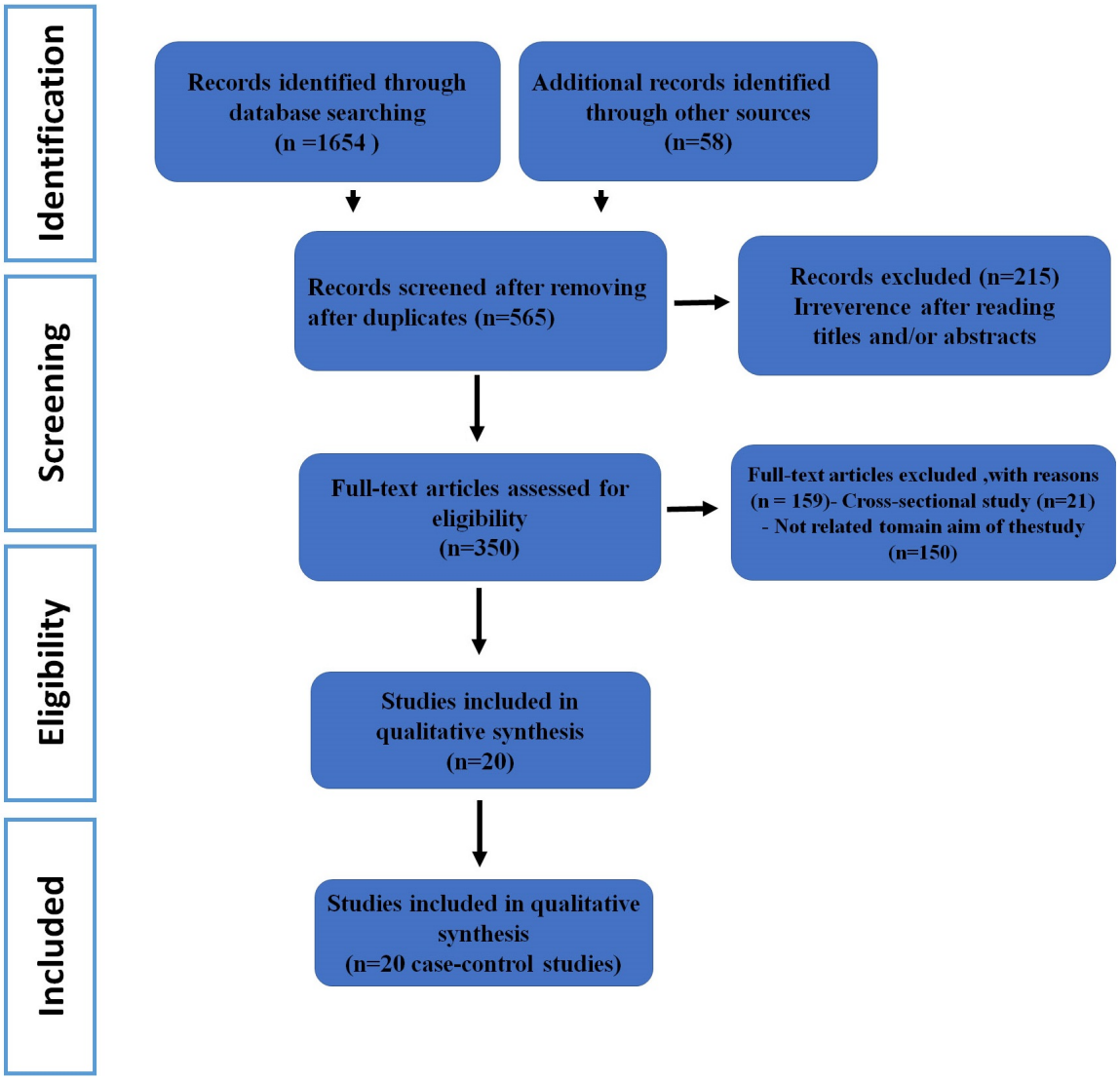

Figure 1: Flow chart of the literature search strategy and study selection.

This suggests that the process of cryopreservation (freezing and storage) does not significantly compromise the engraftment potential of HSCs in the context of autologous transplantation.

However, it is noteworthy that a subset of studies observed higher engraftment rates with non-cryopreserved HSCs, while others reported superior engraftment with cryopreserved HSCs.

These discrepancies may be attributed to variations in patient characteristics, underlying disease types, conditioning regimens, and transplantation protocols employed across the different studies. Such factors can significantly influence the engraftment kinetics and overall success of the transplantation procedure. The mixed findings highlight the complexity of HSC transplantation and underscore the need for further research to elucidate the impact of cryopreservation on engraftment outcomes fully. Careful consideration of patient-specific and procedural variables is crucial in optimizing engraftment rates and improving the success of HSC transplantation, regardless of whether the transplanted cells are cryopreserved or not [34-42].

Cryopreservation Challenge

Cryopreservation, the process of freezing and storing stem cells at ultra-low temperatures, has been the standard procedure for preserving stem cells for transplantation. However, recent studies have revealed that the cryopreservation of stem cells collected from patients with multiple myeloma poses unique challenges.

The disease itself, along with the prior exposure to chemotherapy, affects the quality and functionality of the stem cells, making them more susceptible to damage during the freezing and thawing process [43-48].

The underlying multiple myeloma disease, along with the patients' prior exposure to intensive chemotherapy regimens, can significantly affect the quality and functional characteristics of the harvested stem cells [5, 6]. This compromised stem cell quality makes them more susceptible to damage during the complex processes of freezing and subsequent thawing.

Factors Affecting Cryopreservation

Cryopreservation in multiple myeloma patients is influenced by various factors that can impact the success of the process and subsequent transplantation outcomes. The disease itself affects the bone marrow microenvironment, potentially reducing the quality and quantity of collectible stem cells. Additionally, prior chemotherapy treatments can further compromise the viability and functionality of these stem cells, making them more susceptible to damage during the cryopreservation process. These combined factors increase the risk of complications post-thaw and reduce the efficacy of autologous transplantation in myeloma patients. To ensure successful cryopreservation, it is essential to use proper equipment such as the MVE CryoShipper CX and Thermo Fisher CryoExtra Cryogenic tank to maintain cryogenic temperatures during transportation and storage, thereby preserving the integrity of the stem cells [49]. Moreover, familiarity with contemporary cryopreservation reagents and processes is crucial for understanding their impact on stem cell survival and behavior post-cryopreservation [50]. Addressing challenges in preserving mesenchymal stem cells effectively for clinical applications is also a key consideration [51]. In conclusion, optimizing cryopreservation protocols and techniques while maintaining the quality of stem cells during the process is vital for enhancing the success of autologous transplantation in multiple myeloma patients [51-53].

Alternative Approaches

To overcome the challenges associated with freezing stem cells, researchers and clinicians are exploring alternative approaches. Developing techniques for immediate use of fresh stem cells without cryopreservation: This method involves collecting and processing stem cells shortly before transplantation, eliminating the need for freezing and thawing. While it requires efficient coordination between harvesting and transplantation, it offers the potential for improved outcomes by preserving the functional properties of the stem cells [51-53]. Utilizing advanced biopreservation techniques to improve the success rate of frozen stem cells: Researchers are exploring the application of cryoprotectants and innovative freezing protocols to enhance stem cell survival and functionality after thawing. Using advanced biopreservation techniques to improve the success rate of frozen stem cells, researchers are investigating the use of cryoprotectants and novel freezing protocols to enhance stem cell survival and functionality after thawing [38, 45, 54].

Specific criteria for non-cryopreserved stem cell therapy may include patients who are unable to tolerate the extended preparation time required for cryopreservation. The decision to use non-cryopreserved stem cell therapy should be made on a case-by-case basis, considering the patient's individual characteristics and medical history [11, 12, 14, 20, 55-60].

The patient selection criteria for stem cell transplantation can vary depending on the specific treatment protocol and the healthcare facility performing the procedure. Therefore, patients should consult with their healthcare

provider to determine their eligibility for non-cryopreserved stem cell therapy in the treatment of multiple myeloma [61, 62].

On-cryopreserved peripheral stem cell autografts for multiple myeloma and lymphoma in developing countries can provide a potentially viable treatment option in resource-limited settings. Autologous stem cell transplantation (ASCT) is a procedure that involves collecting a patient's stem cells, treating them with chemotherapy or radiation to eliminate cancer cells, and then reinfusing the stem cells back into the patient's body to restore blood cell production [63-65].

In developed countries, cryopreservation (freezing) of stem cells is a widely adopted practice to facilitate their preservation for future therapeutic use. Cryopreservation enables the long-term storage of collected HSCs, providing flexibility in treatment scheduling and logistical planning for transplantation procedures. However, the implementation of cryopreservation techniques requires specialized infrastructure, equipment, and technical expertise, which may not be readily available or accessible in developing healthcare settings due to financial constraints or limited healthcare resources. The lack of cryopreservation capabilities in resource-limited regions can pose significant challenges in delivering timely and effective stem cell-based therapies to patients who may benefit from them [66-69]. High-dose therapy followed by HSCT is the standard treatment approach for patients with MM. In our recent study, we examined 38 MM patients who underwent autologous peripheral stem cell transplantation using non-cryopreserved cells between 2004 and 2010. The findings showed that all patients achieved successful engraftment, and 76.3% remained alive and disease-free after a median follow-up of 31 months. This treatment approach was associated with a low risk of transplant-related mortality and demonstrated significant therapeutic benefits, making it a safe and effective option for MM patients. This non-cryopreserved HSCT approach simplifies the procedure and increases accessibility for a larger patient population while providing outcomes comparable to other studies [70]. Additionally, the use of non-cryopreserved HSCT has been reported in patients with Hodgkin lymphoma [71].

In conclusion, preserving and storing stem cells for autologous transplantation in patients with multiple myeloma faces unique challenges. The disease itself and prior chemotherapy treatments can negatively impact the viability and quality of the patient's stem cells. As a result, the conventional cryopreservation method for stem cell storage has been found to be less effective in these cases. However, researchers are actively exploring alternative approaches to overcome these challenges. One strategy is the immediate use of fresh, non-cryopreserved stem cells, avoiding the need for long-term storage.

Additionally, advanced biopreservation techniques are being investigated as potential solutions to improve stem cell preservation. These innovative efforts aim to increase the success rates of autologous stem cell transplantation and improve the overall outcomes for patients with multiple myeloma. Continued research and collaboration in this field hold promise for further advancements in stem cell preservation and transplantation, ultimately benefiting those battling this complex and challenging disease.

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