

Stem cell transplantation therapy for acute myeloid leukemia

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Abstract. Acute Myeloid Leukemia (AML) is an aggressive hematologic malignancy, presenting a significant challenge in the field of medicine. In this context, Hematopoietic Stem Cell Transplantation (HSCT) has garnered widespread attention as a potential therapeutic approach. This paper reviews the current research progress in the field of AML treatment, with a specific focus on the application of HSCT. Through a comprehensive analysis of recent literature and clinical trials, it systematically summarizes the therapeutic effects of HSCT in different patient populations. Despite demonstrating certain efficacy in AML treatment, there remain research gaps in the application of HSCT, particularly in specific patient groups and contexts. This paper extensively discusses the principles, types, and application scenarios of HSCT in AML patients. By reviewing recent research findings, this article analyzes the treatment outcomes of HSCT in both young and elderly patients and compares relevant survival data. This paper presents future prospects for research, including in-depth investigations into novel HSCT treatment strategies, the impact of age differences on treatment outcomes, and more. These prospects aim to provide more precise directions for improving the therapies for AML patients.

Keywords: Stem cell; AML; transplantation.

1. Introduction

AML is a bone marrow disease characterized by the excessive proliferation of tumor clone bone marrow stem cells due to genetic changes in blood cell precursors, leading to a disruption of hematopoietic stem cells. It is a complex and heterogeneous disease, and its incidence is increasing with the aging population. AML accounts for only 1.2% of all newly diagnosed cancers in the United States every year. Relatively speaking, it can be considered a rare cancer, but it constitutes one-third of all leukemia diagnoses.[1]

For the majority of the past, both treatment methods and the survival curves of patients have remained stagnant. However, in recent years, novel and highly active therapies for various hematologic malignancies have been approved, among which stem cell transplantation therapy for AML has gained considerable attention. HSCT has consistently been a crucial approach in treating various hematologic malignancies. Despite conventional chemotherapy achieving a complete remission rate of approximately 70% to 80% in AML patients, stem cell transplantation remains a critically important treatment strategy for AML patients.[2]

Stem cell transplantation is a technique used to restore hematopoietic stem cells destroyed by high-dose chemotherapy and radiation drugs used in cancer treatment. Hematopoietic stem cells used for transplantation are typically derived from the bone marrow, blood, or umbilical cord. Stem cells have the ability to differentiate into specific cells and self-renew, serving as carriers in the cancer treatment process. This paper aims to explore the application of stem cell transplantation technology in the context of AML, including treatment advancements, outcome assessments, and future research directions.[3]

2. Pathophysiology of AML

2.1. Pathogenesis of AML

The main cause of AML is gene mutations in hematopoietic genes. Although the exact cause of the mutation is still under investigation, according to the survey results, the probability of mutation is related to environmental factors to a certain extent, including radiation, use of chemotherapy drugs, etc. [4] These mutations result in the inability to produce red blood cells, which further leads to bone marrow failure and severely affects the patient's survival. Additionally, AML can evolve from other diseases such as myeloproliferative disorders (MPD), myelodysplastic syndromes (MDS), paroxysmal nocturnal hemoglobinuria, and aplastic anemia. Recent research suggests that AML may also arise from genetic changes in recurrent hematopoietic stem cells that accumulate with age. Researchers believe that the investigation of AML causes should also consider familial factors related to genetic mutations.[5]

AML, as a highly heterogeneous disease, exhibits a high likelihood of relapse, and prognosis is complex and variable. The pathogenic factors of acute myeloid leukemia can be categorized into genetic mutations, chromosomal translocations, etc. Studies have shown that approximately 97% of AML cases involve genetic mutations. [6] From a cytogenetic perspective, AML can be classified into favorable, intermediate, or unfavorable risk groups, providing valuable insights into the prognosis of AML treatment. For instance, patients with t(9;11), chromosomal 5 or 7 abnormalities, and normal cytogenetics (CN-AML) are considered to have an intermediate risk, while those with chromosomal translocations t(8;21), t(15;17), or inv(16) have a favorable prognosis.[7]

One of the most common genetic mutations in AML is the NPM1 mutation, present in approximately 25% to 30% of AML patients, predominantly in females. This mutation is associated with a monomorphic cell morphology in clinical presentation and exhibits a certain degree of chemosensitivity in both younger and older patient populations.[8]

Internal tandem duplications (ITD) and tyrosine kinase domain (TKD) mutations involving the FLT3 gene are found in 20% of AML cases and 30% to 45% of CN-AML patients. FLT3 is a crucial gene highly expressed in hematopoietic stem cells, and ITD and TKD mutations activate FLT3 signaling, promoting explosive proliferation. FLT3-mutated patients may experience severe Common mutations in AML cases involve FLT3, TKD, TKI, etc., accounting for about 20% of AML cases and 30%-45% of CN-AML patients. IDH mutations are more common in elderly patients, accounting for 15%-20% The pathogenesis of AML is related to mutations in this gene, which have oncogenic properties. In addition, the transcription factor RUNX1 of the Runt gene located on chromosome 21 also plays an important role in its pathogenesis. Its translocation with the ETO/RUNX1T1 gene on 8q22 can lead to AML-ETO. [9]

2.2. Classification of Diseases

As shown in figure1, the revised fourth edition of the WHO classification for AML was published in 2016 and released in book form in 2017. The WHO classification for AML draws upon the FAB classification devised by cytologists in 1976, while defining disease categories based on cellular genetics abnormalities, mutation profiles, and patient histories, forming a unique yet intricate hierarchical structure.[10]

Recently, the International Consensus Classification (ICC) for AMLs have been confirmed. One major change involves the incorporation of AML types associated with blasts and changes in bone marrow proliferation, and the creation of new AML types with genetic abnormalities related to bone marrow proliferation, as well as AML types with mutations in TP53. The classifications by the WHO and ICC define certain AML types using different blast thresholds. While the WHO does not set a minimum threshold for defining genetic abnormalities in AML, the ICC requires a blast percentage of at least 10% in the bone marrow or peripheral blood when defining AML with recurrent genetic abnormalities. [11] Additionally, in the 10-19% blast category in bone marrow or peripheral blood,

the ICC introduces a new category of AML, considering these patients to share some degree of similarity in biological and clinical aspects with those having 10% or more bone marrow blasts. The International Consensus Classification for acute leukemias represents a more in-depth classification in terms of genetic definition, and through collaboration with clinical physicians via the Clinical Advisory Committee (CAC) process, significant progress has been made in understanding the molecular patterns of AML.

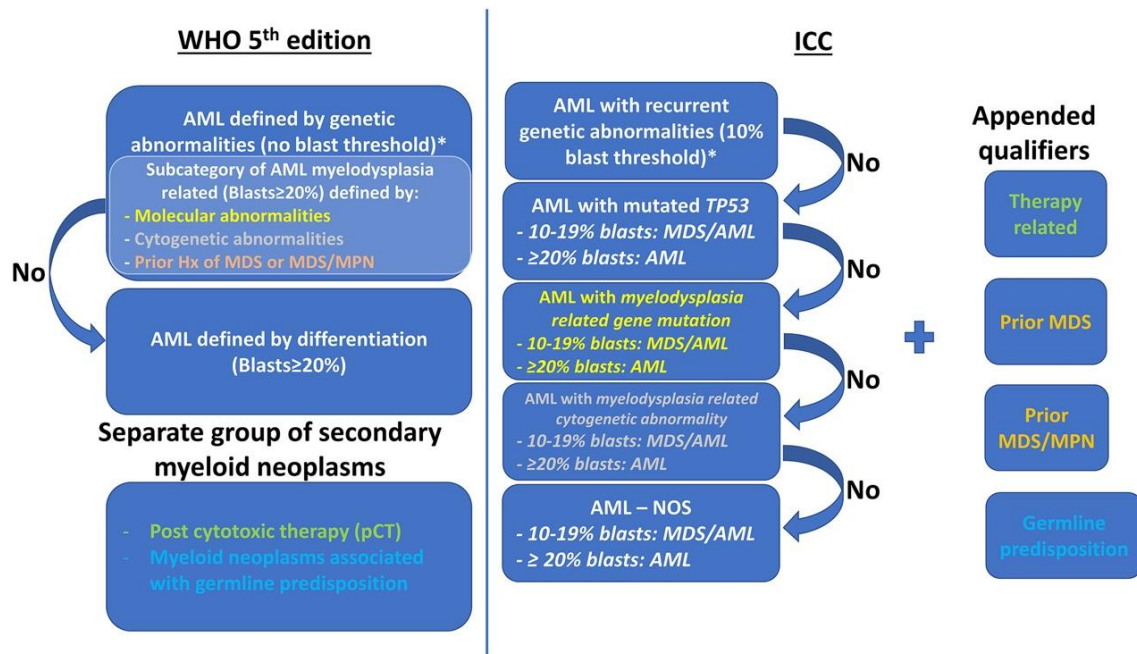


Figure 1. Classification of AML from WHO [12].

3. Principles of Stem Transplantation

3.1. Transplantation Principles and Mechanism

HSCT is a process with intricate steps. Firstly, hematopoietic stem cells are harvested, and these cells primarily come from bone marrow, peripheral blood, or umbilical cord blood for transplantation. Subsequently, patients undergo conditioning regimens, where the purpose of pre-transplant conditioning is to eliminate the host's immune system, eradicate or replace it with the donor's immune system, ensuring the successful engraftment of donor hematopoietic stem cells. There are generally three types of conditioning regimens: myeloablative conditioning, reduced-intensity conditioning, and non-myeloablative conditioning. Myeloablative conditioning aims to control the disease to the maximum extent while reducing the risk of relapse. Following that, hematopoietic stem cells are infused, leading to the regeneration of a new hematopoietic and immune system.

3.2. Types of Stem Cell Transplants

Stem cell transplantation can be categorized into autologous transplantation and allogeneic transplantation based on the source of the donor. The significant advantage of autologous transplantation lies in ensuring that the patient's body will accept the transplanted stem cells since these stem cells are extracted from the patient themselves, reducing the risk of immune rejection reactions.

The allogeneic transplantation of donor stem cells is similar to autologous transplantation. There are two main advantages to allogeneic stem cell transplantation. Firstly, during the process of allogeneic stem cell transplantation, a certain number of immune cells enter the patient's body along with the stem cells, assisting the recipient's body in combating cancer cells—a phenomenon known as the "graft-versus-disease effect." The second advantage is that, unlike autologous transplantation,

allogeneic transplantation involves extracting stem cells from a healthy donor. However, a major drawback of allogeneic transplantation is the potential for the "graft-versus-host effect," where the donor's immune cells may attack the recipient's tissue cells. While mild acute graft-versus-host effects may cause rashes without impacting the success of the transplant, severe cases could be life-threatening. [13] Chronic graft-versus-host effects persist for an extended period, resembling an inflammatory immune reaction that affects recipient tissue cells, leading to complications such as breathing difficulties, joint pain, diarrhea, or adverse effects on organs like the liver. Patients with chronic graft-versus-host effects may need long-term medication to alleviate immune rejection reactions.

To prevent severe transplant rejection, it is crucial to find a stem cell donor whose tissue type closely matches that of the recipient. The most ideal donor is an identical twin, and close relatives' stem cells can also be considered for transplantation. Many national and international databases have been established to help individuals in need of stem cell transplantation find suitable donors.

4. Application of HSCT in the Treatment of AML

4.1. alloHSCT in Elderly Patients

The treatment of AML in elderly patients remains a challenge due to their increased vulnerability and more severe medical conditions. alloHSCT represents one of the best chances for curing AML, albeit with significant toxicity. Research in the past decade has made some progress, suggesting that alloHSCT may be a feasible treatment for elderly AML patients. However, numerous challenges persist, including treatment toxicity, the risk of graft-versus-host disease (GVHD), and the need for prolonged immunosuppression.

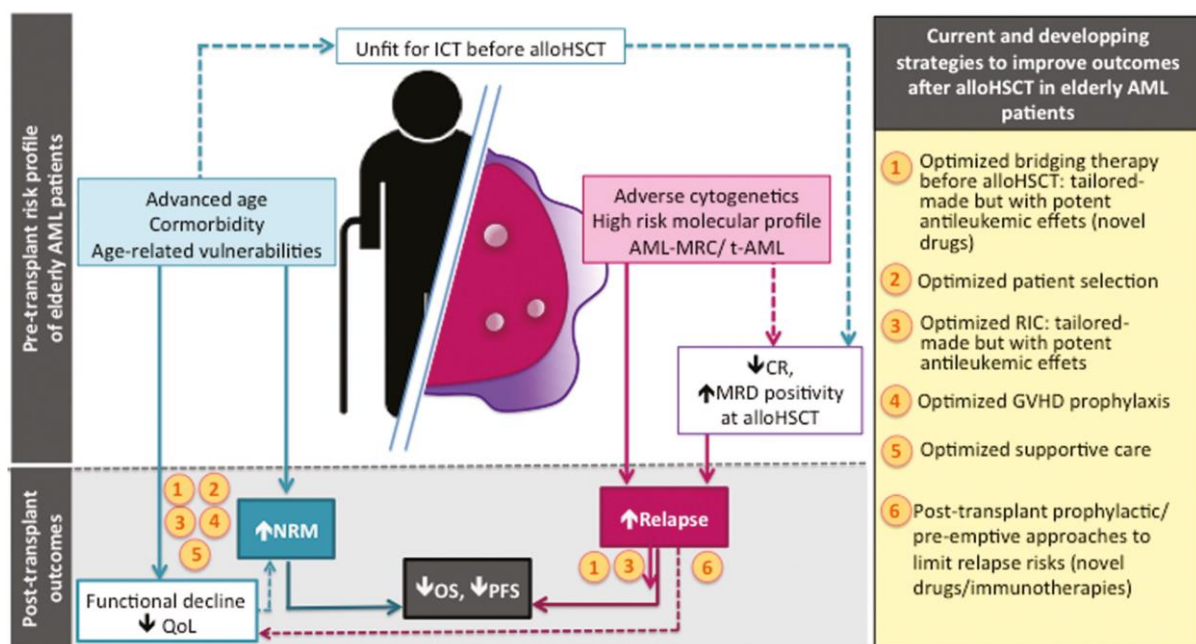


Figure 2. alloHSCT in elderly patients [14].

As shown in figure 2, while some studies indicate that alloHSCT may be beneficial in improving the survival rates of elderly AML patients, further research is needed to clarify the optimal treatment strategies. Additionally, the side effects such as GVHD, infections, and the impact on quality of life (QoL) should be considered. The decision to undergo alloHSCT should involve a careful assessment of the balance between treatment benefits and risks, taking into account the possibilities of long-term disease control, survival, and the potential adverse effects on the patient's QoL.[15]

In recent years, research on the use of alloHSCT for the treatment of elderly AML patients has been increasing. A meta-analysis in 2016 summarized the results of 13 studies, including 749 patients aged

over 60, reporting a 3-year overall survival (OS) of 38% and a progression-free survival (PFS) of 35% after alloHSCT. Recent studies analyzing results from elderly AML patients (50-79 years old) undergoing HLA-matched donor transplants between 2004 and 2014 showed 2-year OS and PFS rates of 50% and 44% for those aged 50-69 and 38% and 33% for those aged 70 and above, respectively. These survival rates align with data from the Center for International Blood and Marrow Transplant Research (CIBMTR). Despite indicating lower survival rates in patients aged over 60 or 70 compared to younger patients after alloHSCT, researchers still consider alloHSCT a viable treatment for elderly AML patients, providing a reasonable chance of cure for over one-third of patients selected for this treatment. However, the debate continues regarding whether alloHSCT offers survival benefits over chemotherapy consolidation for elderly AML patients who achieved complete remission (CR) previously, as there has been no completed Phase III trial directly comparing these two methods. While some studies support the potential benefits of alloHSCT in preventing AML relapse and improving survival rates, careful consideration of the balance between benefits and risks is crucial when deciding whether to perform alloHSCT in elderly AML patients, taking into account treatment toxicity, the risk of GVHD, and the impact on the patient's QoL. [16] Therefore, the practical benefits of alloHSCT in elderly patients with active or refractory disease remain uncertain and require further exploration through research. In addition, the potential long-term effects of GVHD, infections, and immunosuppression also need to be comprehensively considered in the context of alloHSCT for elderly patients. While some studies suggest that elderly patients may be more prone to GVHD, the conclusion about whether the QoL of elderly patients after alloHSCT is worse than that of younger patients remains inconclusive, necessitating more in-depth research to address this issue.

4.2. Prevention and Treatment of Recurrence of AML after HSCT

4.2.1. Biological basis

Recurrence is the primary cause of HSCT failure. Researchers widely believe that, at the diagnostic stage, mutations in specific genes such as WT1, FLT3, et al. are associated with an increased risk of post-transplant recurrence. [17] Understanding the reasons for relapse of AML after HSCT from a biological perspective is essential to develop effective preventive methods and treatment strategies. The mechanism of relapse after high-cell transplantation differs from that of relapse after chemotherapy. Immuno-evasion mechanisms are correlated with the recurrence of the patient's disease, and studying potential immuno-evasion mechanisms in patients has a positive impact on how to treat and intervene with patients. Immuno-evasion mechanisms primarily include loss of the HLA genomic region, generation and loss of anti-inflammatory or pro-inflammatory factors, inhibition of immune checkpoints, and release of metabolic active enzymes. The loss of the HLA genomic region is the main mechanism of immuno-evasion in HSCT, accounting for 33% of relapsed patients. Loss of pro-inflammatory cytokine IL-15 in myeloid cells may lead to a reduction in the graft-versus-leukemia (GVL) effect.

The role of inhibitory immune checkpoints in post-HSCT relapse is the current focus of research. Studies have found a downregulation of immune regulatory molecules, including PDL-1, on AML cells during relapse after HSCT. PD-1 inhibitors play a crucial role in treating relapse of acute leukemia after HSCT. Nivolumab has been applied to treat cases of Hodgkin's lymphoma relapse after HSCT. In this context, the drug has proven to be an effective treatment option but is accompanied by an increased risk of GVHD, indicating its action through enhancing the GVL effect.

Other potential immune evasion mechanisms in the non-transplant setting include the production of IDO-1, arginase, etc. by leukemia cells, which can further lead to increased levels of adenosine and inosine that lead to immunosuppression, and the consumption of arginine, which is crucial for the regulatory function of T cells, so the post-transplantation environment should pay more attention to potential immune evasion mechanisms and take measures to regulate them.

4.2.2. Cell therapy for recurrence after stem cell transplantation

The recurrence of AML after alloHSCT may be associated with the conditioning chemotherapy received by tumor cells before transplantation and/or the escape from post-transplant immune control mechanisms. These mechanisms limit the immune response against malignant cells, thereby promoting recurrence after HSCT-related GVHD. While past studies have primarily focused on reducing donor T cells to lower the probability of GVHD, research has indicated that T cell depletion may actually lead to graft failure.

Even in HLA-matched HSCT, donor T cells can recognize antigenic structures on the surface of leukemia cells that are not present in the patient's HLA complex. This phenomenon is known as minor histocompatibility antigens, and polymorphism in antigenic peptides can trigger immune responses, even in patients receiving stem cells from HLA-matched donors. Immune escape mechanisms mainly involve the evasion of immune control by tumor cells and the alloreactivity of donor T cells against minor histocompatibility antigens.

Several studies have been conducted to explore the effectiveness of cellular therapy for the recurrence of AML after alloHSCT. Among them, mobilizing cellular immunotherapy, such as lymphocyte infusion (DLI), has been a widely studied approach. Some studies suggest that patients receiving DLI achieve better survival outcomes, particularly when used preventively. Preventive DLI is a proactive strategy, providing DLI promptly upon detecting minimal residual disease or mixed chimerism to prevent AML recurrence. Additionally, preventive DLI has shown better results in patients with lower disease burden, complete remission, and favorable cytogenetics. However, the application of DLI comes with challenges, such as an increased risk of GVHD. Therefore, careful consideration of patient-specific conditions is essential when deciding to use DLI.[18]

5. Conclusion

HSCT plays a crucial role in the treatment of AML. AML, an invasive hematologic malignancy, has long posed a challenge in the field of medicine. HSCT, as a therapeutic approach, involves the introduction of healthy hematopoietic stem cells with the aim of restoring normal hematopoietic function in patients. Considered one of the best opportunities for curing AML, HSCT is particularly valuable for patients who cannot achieve complete remission through traditional treatment methods. By undergoing HSCT, patients can obtain a new and healthy hematopoietic system, providing a potential avenue for disease cure. HSCT demonstrates efficacy in both young and elderly AML patients. Younger patients may achieve long-term survival and complete remission through HSCT, while it is also considered a viable treatment option for elderly patients, despite the increased treatment challenges in this demographic. Although HSCT shows significant therapeutic effects in some AML patients, its application comes with a set of challenges, including treatment toxicity, the risk of Graft-versus-Host Disease (GVHD), and the need for long-term immune suppression in patients. Future research should focus on understanding the advantages, limitations, and potential risks associated with HSCT to develop more precise and effective treatment strategies. Additionally, investigating novel HSCT treatment approaches and considering the specific impact of age factors on treatment outcomes should be key areas of interest. Hematopoietic Stem Cell Transplantation provides a crucial therapeutic opportunity for certain AML patients. However, its application requires careful evaluation of individual patient circumstances, balancing the benefits and risks to formulate optimal treatment plans.

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