Systematic Review

Received: 2023-08-29
Accepted: 2023-10-09

BCCR
2023, No 1, Vol 15 :9-17
www.bccrjournal.com

The effect of Stem Cells in the Treatment of Leukemia

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ABSTRACT

Context: Stem cells play a key role in tissue repair and regeneration due to their self-renewal properties. In recent years, the use of stem cells as an important and valuable treatment method has created a new hope for the treatment of diseases and disorders that were previously difficult to treat. In this review article, the introduction of stem cells and their capabilities for treatment, as well as the sources of stem cells and the use of these sources for the treatment of diseases, including the treatment of leukemia, have been discussed.
Evidence Acquisition: Extensive search in Google Scholar and PubMed using keywords related to the article and review of various articles published between 1957 and 2022 about stem cells and the use of these cells to treat diseases.
Results: Recently, it has been proven that hematopoietic stem cells can be produced from pluripotent embryonic stem cells, and hematopoietic stem cells can make different blood cells. These findings help medical science in the treatment of various types of blood cancer. Also, during the conducted research, it has been determined that induced pluripotent stem cells(iPSCs) can be used in the treatment of various diseases, including leukemia.NOTCH, Wnt, TGF-B1 signaling pathways play an important role in the proliferation and differentiation of hematopoietic stem cells. Evidence shows that cancer stem cells have a high ability to create tumors. The presence of cancer stem cells has been reported in some patients, including those with acute myeloid leukemia.Also, the results of research conducted in recent years show that the SALL4 gene can be used in the treatment of leukemia.
Conclusions: The results of various researches show that treatment with stem cells, including hematopoietic stem cell transplantation, can be a suitable method for treating patients with leukemia.

Keywords: stem cell, leukemia, Hematopoietic stem cells (HSCs), induced pluripotent stem cells (iPSCs), differentiation

INTRODUCTION:

1. Context

Today in the world, cancer immunotherapy and treat¬ments based on stem cells have received a lot of at-ten-tion. many clinical studies have been conducted on them and these researches are still ongoing. Cancers are (i) solid (ii) liquid. Compared to (i) the treatment options for (ii) are small; with grave prognosis being the average. Leukemia is 'liquid cancer'. In this article, an attempt has been made to investigate the effect of stem cells in the treatment of leukemia. Stem cells are undif¬ferentiated cells that can transform into other types also having the ability to reproduce and renew themselves. Thus the 'stems' offers scope for 'regener-ative therapies'. These cells (juvenile stage) have great ability to migrate to required (pathology) site; to self-al-ter to the affected\damaged tissue and the potential for repair and regeneration. Such ability to differen¬tiate into a specialized adult cell and because permanent self-re¬generation are the two main characteristics of a stem cell (1, 2, 3, 4). Human pluripotent stem cells (HP¬SCs) and mesenchymal stem cells (MSCs) are the two main types of stem cells (2, 3, 4). Bone marrow is one of the best source for the stem cells.(2)

Human physiology also has multi-potent stem cells. These have lineage limitation i.e., their ability to trans-form to other cell types is limited; so also to propagate alias are Low Potency Stem Cells. And whereas, HP-SCs can propagate & transform into any cell in the body at any anatomical location alias are High Potency Stem Cells. HPSCs exist in the fetus for a short period of time, and after that pluripotent stem cells become multipotent stem cells and then form different tissues of the body (5). Research shows that stem cells may be changed by various factors, such as environmental and genetic fac¬tors, and in this case, cancer occurs. Can-cer is one of the dangerous diseases that threatens the health of societies around the world. In status cancer, cells grow abnormal¬ly and these cells may have the ability to spread and be transferred to other tissues and parts of the body (1).

In leukemia, white blood cells are formed in large num¬bers mostly un-formed which all cannot function properly, these abnormal cells can destroy healthy red and white blood cells and the platelets in the bone mar-row, resulting in leukemia symptoms (immunity sys-tem attacking the human circulatory system; haemo-poiesis; blood production marrow-&-hollowed bones; etc.) clinically manifesting as hematoma - bleeding problems, severe and continuous fatigue, bruised skin, severe and sudden weight loss, swollen lymph nodes, frequent or severe infections (1).

Chemotherapy, surgical and radiotherapy methods which are among the common methods in cancer treat¬ment, cause problems apart damage to other tissues and recurrence of the disease. Specially in leu-kemia(s) most such type of interventions end up with confounding; conflicting and contradictory results. In this regard, from caption perspective the so-called low potency stem cells from the (sources : abundant in Haem parynchema peripheral\circulating whole blood, bone marrow and umbilical cord blood) Hematopoie-tic stem cell alias 'blood cells' shall be focused upon for the benefit of the clinical & scholarly community's benefit.

The first stem cell therapy was performed in 1956 by E. Donnall Thomas, which included bone marrow trans-plantation to treat leukemia and in 1998, stem cells were isolated from human embryos by James Thom¬son. After that, this method gradually improved and was used in the treatment of other diseases, For ex-am¬ple, in 2017, induced pluripotent stem cells (iPSCs) of retinal cells were used for the treatment of macular degener-ation for the first time (2, 4, 6). Multipotent stem cells have been used in the treatment of leukemia since the 1960s (5). iPSCs are made in labs. If cancer immunotherapy can be developed based on stem cells it can be very effective in treating all types of cancers, including leukemia; lead to real time anti-degenerative & pro-regenerative medicines.

Cancer is on the rise. The purpose of this article is to succulently introduce and review stem cells; their types; with Leukemia as focus.

Table 1. Types of stem cells and their description

	Types of stem cells	Description
1	Totipotent cell	They have the ability to transform into different types of human cells (the ability to create the whole organism)
2	Pluripotent cell	They have the ability to transform into different types of cells except the external tissues of the embryo and the placenta
3	Multipotent cell	They have the ability to transform into limited population of cells
4	Unipotent cell	They have the ability to become only one type of cell

2. Evidence Acquisition

The data for the present review were accessed through different publications and database including ISI, SID, and PubMed.

2.1. Search strategy

The data for this narrative review study were obtained from Science Direct, PubMed, Google Scholar, and Scopus. To provide a thorough and all-encompassing view of the research conducted on this topic thus far, publications from 1957 to 2022 were searched without any temporal constraint.

3. Results

3.1. Stem cells

Stem cells, which are also known as mother cells, have the ability to create different types of cells in the body, for example, they can become insulin-producing cells, nerve and heart cells. Stem cells function by self-renewal and reproduction by mitosis. When tissue damage occurs, stem cells can help repair injuries and heal wounds (3, 5, 7). These cells are classified into different categories, including totipotent stem cells, pluripotent stem cells, multipotent stem cells, and unipotent stem cells. (Table1) Totipotent stem cells are the most diverse types of stem cells, these cells can become all human cells, such as blood, brain and heart cells. Totipotent stem cells have the ability to create the entire functional organism. Even though pluripotent stem cells can create different types of cells and tissues, they cannot create the entire organism. Multipotent stem cells become more limited populations of cells. Unipotent stem cells can only make one type differentiated cell (3) . The use of stem cells has created new horizons for the treatment of various diseases, including incurable diseases such as cancers and congenital disorders. Today, scientists and doctors around the world study and conduct numerous experiments related to these cells (6).

3.2. Choosing the source of stem cells for cancer treatment

The source of stem cells can be classified into two main sources: the perinatal sources and the adult sources (Figure 1). The adult source of mesenchymal stem cells can be obtained in the form of tissue from a person, such as peripheral blood, liver, muscle, dental pulp, bone marrow, etc. The perinatal source of mesenchymal stem cells includes: placenta, umbilical cord, Wharton jelly, cord blood, amnion and chorionic membrane (2, 8) .

Bone marrow is the first source and one of the best sources of mesenchymal stem cells. In humans, mesenchymal stem cells are usually isolated from the bone marrow of the pelvis, femur and tibia, but it should be noted that the use of bone marrow as a source of mesenchymal stem cells compared to the use of an embryonic source such as the umbilical cord has defects and It has problems such as: the possibility of viral contamination and also the invasiveness of the sampling method , But using umbilical cord blood for various reasons such as easy access and non-invasive sampling method can be a good alternative instead of using bone marrow as a source of mesenchymal stem cells (9) .

3.3. Cancer stem cells

Cancer stem cells (CSCs) are a small subset of tumor cells. These cells can differentiate into different cell lines(10). Also, these cells have a great ability to create tumors. The presence of CSCs has been observed in pa-

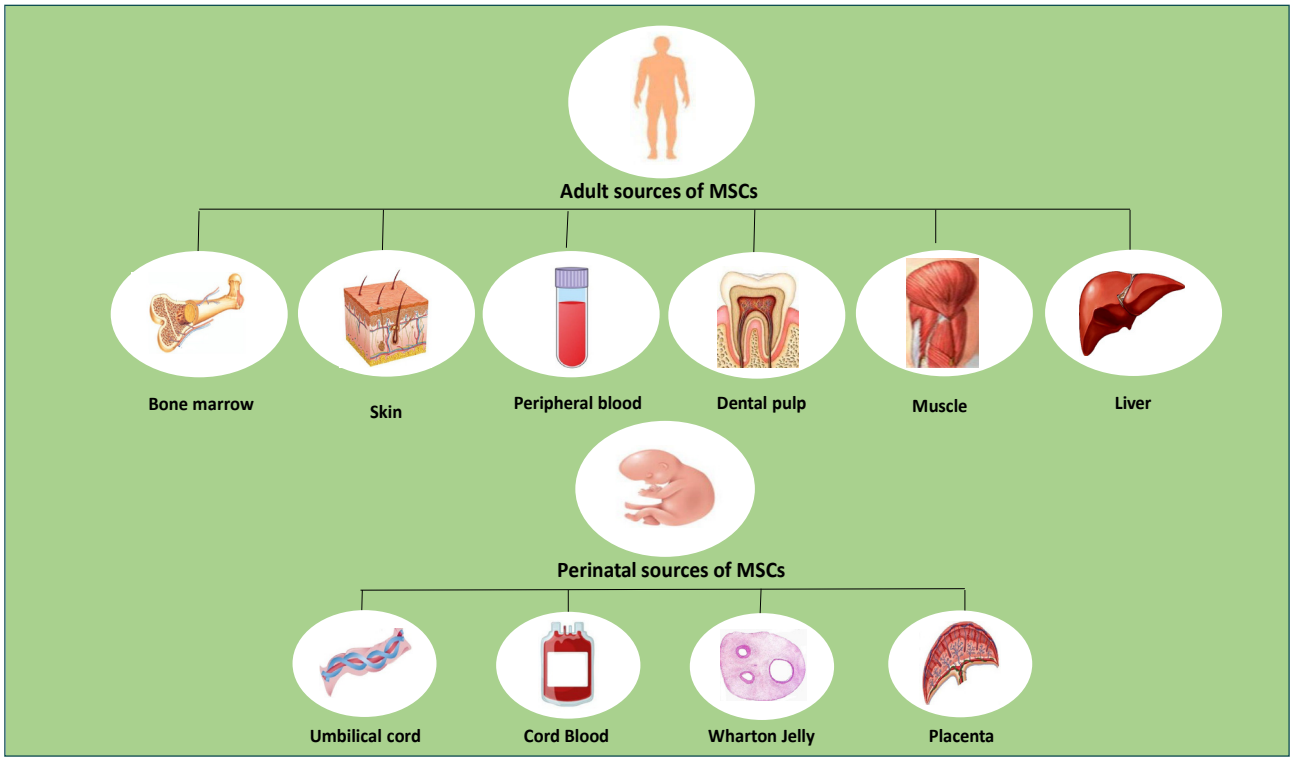

Figure 1. Sources of Mesenchymal stem cells (MSCs): Perinatal source, adult source. Perinatal sources include: placenta, umbilical cord blood, Wharton's jelly, etc. Adult sources include: bone marrow, muscle, dental pulp, liver, peripheral blood, skin, etc.

Table 2. cancer stem cell markers in Acute myeloid leukemia and Bone marrow cancer

Cell surface markers	The type of tumor
	CD34+
Acute myeloid leukemia	CD71 -
	CD38 -
	CD90 -
	CD117 -
	CD123+
Bone marrow cancer	CD138 -

tients with acute myeloid leukemia (AML) and in other patients with tumors of the pancreas, liver, intestine, and brain(11). It has been observed that because cancer stem cells remain after treatment, there is a possibility of resistance to chemotherapy and tumor recurrence(12, 13). To identify and isolate CSCs, cell surface markers as well as aldehyde dehydrogenase enzyme activity are very important. Several methods are used to identify CSCs. Isolation and identification through expression of cell surface markers and aldehyde dehydrogenase enzyme activity are common methods. The method of identifying CSCs through the expression of cell surface markers is based on the presence or absence of cell surface markers, for example, CD34+, CD71-, CD90- and CD38- are among the markers for identifying cancer stem cells, acute myeloid leukemia and CD138- is a marker for bone marrow cancer stem cell identification (Table 2). It may be possible to prevent recurrence of the disease by target-

ing these markers and specifically destroying these cells. Currently, the study of these markers and their role in the treatment of leukemia is an active research area in the world(11, 13).

In the method of identifying CSCs through the activity of Aldehyde Dehydrogenase (ALDH) enzyme, ALDH enzyme is used and its activity level is measured by Aldefluor method. By catalyzing the conversion of aldehyde to carboxylic acids, ALDH maintains cell homeostasis and plays an important role(14). Using the Aldefluor assay, which is a non-immunological fluorescent system and a practical method, it is possible to identify living cancer stem cells with a healthy plasma membrane in the tissues(15).

3.4. Production of hematopoietic stem cells from human embryonic stem cells

In treatments that are based on cell transplantation or when regeneration of damaged cells and damaged tissue is considered, embryonic stem cells are considered one of the important sources and in the future, new treatment methods can be developed using these cells. Presented, but these cells may divide uncontrollably due to chromosomal displacement or mutation and cause various cancers, which can cause problems. In recent years, research and studies have been done to produce hscs from pluripotent ESCs (1, 10, 11). Hematopoietic stem cells can make different types of blood cells, these cells multiply in the bone marrow. Today, hematopoietic stem cells can be expansion in ex vivo culture (9, 12) .

Hematopoietic stem cells are classified into two groups:

1. Hematopoietic stem cells with long-term growth ability (LT-HSC), because this type of hematopoietic cells have unlimited self-renewal ability, these cells are called (LT-HSC).

2. Hematopoietic stem cells with short growth ability (ST-HSC), these cells have limited self-renewal ability and are obtained from (LT-HSC) (12).

For mesenchymal stem cell proliferation and cell cycle completion, Runx1 is used as a transcription factor, and low expression of Runx1 can cause cell cycle arrest. The TGF-B pathway is a regulatory and inhibitory pathway for the proliferation of mesenchymal stem cells. NOTCH and Wnt signaling pathways play an important role in cell differentiation, survival and proliferation of cells, including hematopoietic stem cells. CD34+ is a cell adhesion factor and plays a role in stem cell attachment to bone marrow stromal cells, this attachment regulates the cell cycle and cell survival (1, 9, 13, 14) . SALL4 is a member of the SALL family. It has been found that SALL4 plays an important role in the self-renewal of embryonic stem cells. Normally, this gene is not found in tissues after birth, but it can be re-expressed in cancer cells (16). Research has shown that the SALL4 ESC gene can be used in the treatment of leukemia (1).

3.5. Production of hematopoietic progenitor cells from induced pluripotent stem cells

According to the results of experiments and research conducted by Yamanaka and Takahashi, it was found that cultured mouse fibroblasts can be transformed into induced pluripotent stem cells (iPSCs) in the laboratory and these cells can be used to treat many diseases. iPSCs have the ability to create a complete organism (17, 18). Unlike embryonic stem cells, ipscs have immunological problems and the risk of transplant rejection is very low, and the use of ipscs, unlike the use of embryonic stem cells, does not have ethical problems. iPSCs can be produced from a patient and those special iPSCs produced can be used to treat the same patient(17, 19). Also, during experiments conducted in 2006, it was found that if the gene set that includes KLF4, OCT4, SOX2 and C-MYC genes is transferred to mouse fibroblasts, cells are produced that are very similar to embryonic stem cells, these cells were called iPSCs (17) .

The production of hematopoietic progenitor cells from induced pluripotent stem cells can be a great help in the treatment of diseases. Researchers discovered that iPSCs can be used in the treatment of diseases such as Chronic Myelogenous Leukemia (CML) and Acute Myeloid Leukemia (AML) (1).

3.6. Abnormalities of hematopoietic stem cells in leukemia

The correct reproduction of hematopoietic stem cells plays an important role in the production of blood cells. Chronic myeloid leukemia (CML) and acute my-

eloid leukemia (AML) are both types of blood cancer. AML has an acute course and affects myelocytes, also this disease may originate from HSCs. Mutations and chromosomal translocations can cause AML. CML has a chronic process and affects myelocytes (myelocytes make red blood cells, platelets, white blood cells except lymphocytes). The cause of CML is the presence of the Philadelphia chromosome in the bone marrow and blood of patients with this disease. The Philadelphia chromosome is a defective chromosome and it is created as a result of mutual transfer of parts of chromosome 9 and chromosome 22 t(22;9) , and the ABL gene on chromosome 9 is connected to the BCR gene on chromosome 22 , and chromosome 22 has the BCR-ABL gene sequence (1, 20, 21).

The GATA-1 protein is important for the formation and maturation of red blood cells, megakaryocytes, and the mutation of this gene is seen in acute megakaryoblastic leukemia and can affect the hematopoietic transcription factor (1).

3.7. Transplantation of hematopoietic stem cells for the treatment of leukemia

HSCT can be a promising treatment for some diseases such as AML, CML, ALL (22, 23). Also, in many countries, HSCT is used in the treatment of some diseases such as blood malignancies and autoimmune diseases. Research on HSCT from 1950 to 1970 by a research team at the Fred Hutchinson Cancer Research Center showed that bone marrow cells can be injected intravenously and these new bone marrow cells replace the old bone marrow cells and they can produce new cells (24).

Different types of bone marrow transplant are: allogeneic transplant and autologous transplant.

In autologous bone marrow transplantation, the transplanted tissue is removed from the patient and the malignant cells are destroyed by some anti-cancer drugs, and then the received transplanted tissue is re-injected into the patient's body. The risk of infection as well as the risk of transplant rejection is low in this type of transplant (25).

Autologous transplantation can be used in the treatment of multiple myeloma (MM) and Hodgkin's lymphoma (HL) should be used (1, 26, 27).

According to the studies, the probability of GVHD for patients with myeloma who undergo autologous transplantation is between 5-20%, but for patients who undergo allogeneic transplantation, the probability of GVHD is almost 50% (28).

In allogeneic transplantation, the transplanted tissue is not received from the patient himself and the received cells are healthy, for example, the transplanted tissue can be received from the patient's father, mother, brother or sister after clinical tests and examinations. Allogeneic transplantation can be used in the treatment of CML, MM, ALL, AML (1, 29, 30). Allogeneic bone marrow transplantation can also be used in the treatment of NHL (1, 26) .

The type of transplant can be different according to the type of leukemia, for example, according to studies, the course of CML is usually three-phase. Allogeneic transplantation is usually used in the treatment of CML due to chronic phase 1 and TKI intolerance and critical phase. Also, for the treatment of patients with ALL and AML who have a high risk of relapse, allogeneic transplantation is a suitable option(1, 31, 32). It has been observed that the use of allogeneic transplant is less toxic in young patients. Allogeneic transplantation can be used for patients with NHL who have relapsed after autologous transplantation. Autologous transplantation can be used for the treatment of MM and HL due to its low sensitivity to recurrence. It has also been reported that in the case of treating MM and HL with autologous transplantation, the mortality rate and the effects of GVHD are reduced, so it can be a suitable option for the treatment of these patients(1, 26). During the relapse of acute leukemia patients, HSCT can help the survival of these patients. According to the results obtained from a clinical study with an average follow-up period of 61 months on patients with AML with an average age of 38 years and ALL with an average age of 29 years who were treated with HSCT, it was found that in 39% of patients with ALL And in 55% of patients with AML, the time of the first complete recovery was less than 6 months. During this research, in high-risk patients with AML and ALL

who were treated with HSCT, the 3-year survival rate was reported as 6% and 10%, respectively. Also, for low-risk patients, the 3-year survival rate was 42% in AML and 46% in ALL(33).

4. Conclusion

Today, with the discovery of new treatment methods and the use of stem cells, new hopes have been created for the treatment of cancer. It has become possible to treat many diseases, including blood disorders and blood cancers, with stem cells. One of the suitable options is to use Hematopoietic stem cell transplantation (HSCT), which has different types:

1-Allogeneic transplantation

2- Autologous transplantation

As mentioned, the treatment by stem cells is developing and progressing, but there are issues and challenges for clinical treatments using these cells, factors such as the genetic instability of stem cells, the existence of ethical issues and transplant rejection, which has made the work a little difficult. It is hoped that with more studies and research in this field, these problems will be solved and in the future stem cells can be used to treat a wide range of diseases.

Acknowledgements

The authors thank all the individuals who contributed to performing this research.

Footnotes

• Authors' Contribution: K.sh. designed the evaluation and drafted the manuscript; A.N. participated in manuscript writing; A.A. participated in manuscript writing; A.A. Designed the evaluation and drafted the manuscript.

• Conflict of Interests: The authors declare no conflict of interest in this manuscript.

• Funding/Support: Our manuscript did not receive any funding.

Abbreviations

HSCs : Hematopoietic stem cells ; ESCs: Embryonic stem cells ; iPSC : induced pluripotent stem cell ; HSCT: Hematopoietic stem cell transplantation ; MSCs : Mesenchymal stem cells CSCs: Cancer stem cells ; CML : Chronic myelogenous leukemia ; AML : Acute Myeloid Leukemia ; MM : Multiple myeloma ; HL : Hodgkin's lymphoma ; ALL : Acute lymphoblastic leukemia ; NHL : Non-Hodgkin lymphoma ; GVHD : Graft versus host disease

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