Review Article

Applications of Stem Cell Therapy and Gene-Editing Technologies in Leukemia Treatments

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ABSTRACT

Leukemia, especially acute myelogenous leukemia, affects millions across the globe and has been the focus of many new and emerging treatment opportunities, including stem cell therapy. Hematopoietic stem cells, a type of stem cell that eventually develops into blood cells or platelets, have been a crucial part of many of these emerging treatments. This article focuses on how genetic engineering of stem cells can enhance their therapeutic potential in treating various forms of leukemia. Some promising applications of genetically modified stem cells include modifying stem cells with an apoptosis gene to selectively kill the cancerous cells and create a suicide gene mechanism, using modified hematopoietic stem cells (HSCs) to create chimeric antigen receptor T-cells (CAR T-cells), and modifying induced pluripotent stem cell derived natural killer (iPSCs-derived NK) cells to target tumors at multiple antigen sites. In addition to this, this mechanism has shown significant promise in the treatment of leukemic stem cells, which can aid in preventing relapse. Despite major success in the field of genetically modified stem cell (GMSC)-based treatment, more research is needed to determine how this technique can translate to patient-based care and be used in clinical settings.

Keywords: Stem cell therapy; cancer; leukemia; genetically engineered stem cells; CAR T-cell therapy

INTRODUCTION

Stem cell therapy is an emerging new treatment option being pursued to treat a range of diseases, including cancer. The discovery of stem cells dates back to 1981, when Martin Evans, Matt Kaufman and Gail Martin became the first scientists to identify embryonic stem cells (ESCs) in mice (1). James Thomson and John Gearhart isolated the first human ESCs and grew them *in vitro* in 1998. Thomson's research was centered around isolated human ESCs from blastocysts (2). John Gearhart's research was focused on isolating pluripotent stem cells from human primordial germ cells (3). In 2006, stem cell research was revolutionized when Shinya Yamanaka and his team discovered a way to transform adult cells into embryonic-like stem cells through the introduction of four main genes. Since 2013, scientists have discovered several significant applications of ESCs and induced pluripotent stem cells (iPSCs) in treating various diseases and conditions. Some examples include retinal conditions, cardiovascular issues/research, skin grafts, diabetes management, and cancer. A timeline for the major milestones in stem cell research is depicted in Figure 1.

As stem cell technology grew more advanced over the years, the applications of this technology broadened,

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Accepted September 24, 2025
https://doi.org/10.70251/HYJR2348.35556564

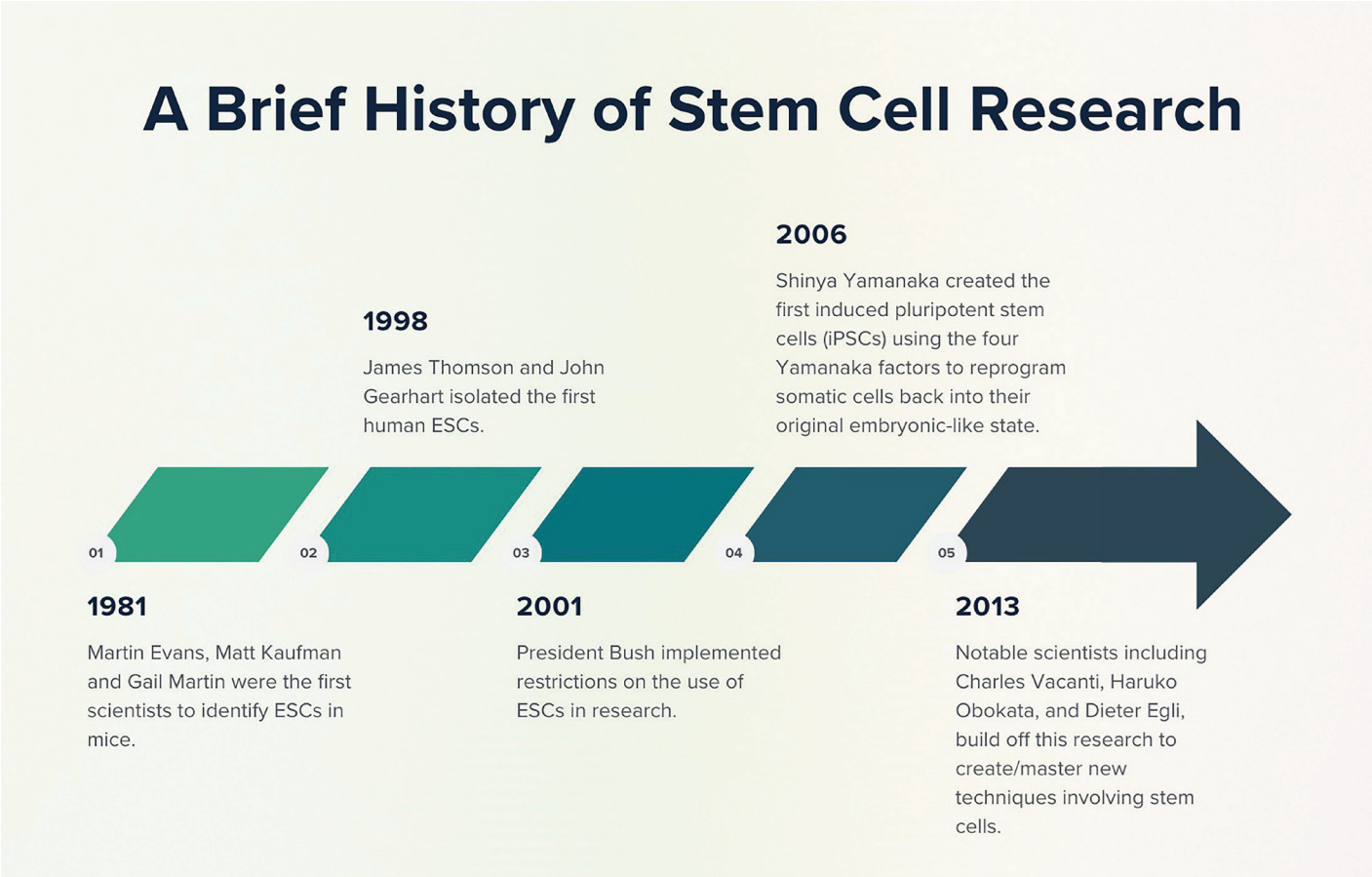

Figure 1. Timeline highlighting major events in stem cell based therapeutic research, including the identification and isolation of ESCs, and development of iPSCs. The Figure ure describes the identification of ESCs in 1981, then moves to when ESCs were first isolated in 1998 and when restrictions on ESCs were first implemented. Then, it describes the creation of iPSCs and discusses notable scientists within the field of stem cell research.

including its role in leukemia treatment. Stem cell therapy has been predominantly explored and utilized for blood cancer types, including leukemia, lymphoma, multiple myeloma, and myelodysplastic syndromes. Stem cell therapy is beneficial because stem cells can be used to help the body produce new healthy blood cells that are damaged by chemotherapy, for instance, in the case of blood related cancers. In case of leukemia, stem cell therapy is able to directly target the tumor (known as graft-versus-tumor), as the white blood cells in the transplant target the cancerous cells (4). They can help regenerate damaged tissue, therefore increasing the effectiveness of other cancer treatments. Many other treatments aren't specific enough to target the tumor site. This reduces their efficacy, increases relapses in metastatic activity, and some types of cancer become resistant to these therapies (5). The objective of this review is to analyze the applications of stem cell and gene-editing technologies in a synchronous manner and detail the efficacy of these treatments in the context of leukemia.

OVERVIEW OF LEUKEMIA

Leukemia is a form of cancer that affects blood cells and blood progenitor cells. It can cause the bone marrow to produce excessive abnormal white blood cells, which can suppress healthy white blood cells, red blood cells, and platelet formation.

Classification of Leukemia

Leukemia is classified into four main categories: acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL),

and chronic myelogenous leukemia (CML).

Acute leukemia refers to when the affected blood cells are blasts (immature blood cells), which multiply rapidly and cause the disease to spread and worsen quickly. Chronic leukemia refers to when the affected blood cells are mature. Chronic leukemia can involve a lack of cell production or an increase in cell production, however these abnormal cells can function normally for a longer period of time, and accumulate much slower, which can cause chronic leukemia to go undiagnosed for years. Lymphocytic leukemia affects the lymphoid cells in lymphatic tissue, which is a part of the immune system, while myelogenous leukemia affects myeloid cells, which further develop into red blood cells, white blood cells, and platelet producing cells (6). This review aims to focus on how stem cell therapies have been used to treat leukemia and explore treatments within the emerging field of genetically modified stem cells.

Diagnostic Assessment of Leukemia

Leukemia is traditionally diagnosed through a combination of multiple tests. Physical exams are primarily conducted by doctors to examine for signs such as fever, shortness of breath, rapid heartbeat, bruising or paleness, swollen/enlarged lymph nodes, and tenderness within the skeletal frame. A complete blood count (CBC) measures the number and quality of white blood cells (WBCs), red blood cells (RBCs), and platelets, as leukemia can affect these results. Blood chemistry tests can reveal how well certain organs are functioning and can help determine the stage of leukemia that is present. Measuring blood clotting factors can also reveal whether leukemia is causing unnatural clotting patterns, and flow cytometry is a more sensitive test used to classify cells using a fluorescent marker. Flow cytometry is useful for determining the specific features of the blasts (leukemic cells) and formulating a specific prognosis (7).

This review aims to focus on how stem cell therapy contributes to the world of cancer treatments.

Unlike other therapeutic options for leukemia treatment, stem cell therapy has the potential to act as a singular treatment that stays in effect throughout a patient's lifetime. This mechanism occurs because stem cell therapy creates an "immunological memory" within the body, which allows it to recognize cancerous cells again after the conclusion of the treatment (8). Stem cell therapy has the ability to revolutionize leukemia treatment, especially through gene editing technologies to target cancerous cells and minimize damage to healthy tissue.

OVERVIEW OF STEM CELLS AND THEIR THERAPEUTIC APPLICATIONS IN LEUKEMIA

There are different types of stem cells used for stem cell therapy; the cell line is selected based on their individual unique properties. Some of these are discussed below:

Embryonic Stem Cells and Adult Stem Cells

ESCs are stem cells derived from the undifferentiated cell mass found in embryos. ESCs can cause tissue rejection in some cases when implanted into the patient's body. Induced pluripotent stem cells (iPSCs) were developed as an alternative to ESCs, which aren't conventionally used in modern cancer treatments (9). Adult stem cells (ASCs) are found in small amounts in different tissues, such as the brain, bone marrow, blood vessels, skin, teeth and heart. The two main properties of adult stem cells are their ability to self-renew, and unlimited potency (10). However, they have limited differentiation (depending on where the cell is found) compared to ESCs. There are multiple types of ASCs, including mesenchymal stem cells, hematopoietic stem cells, neural stem cells, and more. We will briefly discuss some of these stem cells and the novel approaches for utilizing them for therapeutic applications in the context of leukemia.

Hematopoietic Stem Cells (HSCs)

HSCs are multipotent stem cells that develop into different types of blood cells, including platelets, white blood cells, and red blood cells. HSCs are found in the bone marrow and peripheral blood (11).

Hematopoietic stem cells are an emerging treatment for anti-cancer therapies, especially blood cancers such as leukemia. HSC transplantations are administered to patients following a conditioning treatment (generally consisting of varying dosing of chemotherapy, radiation, and immunosuppressive drugs). The goal of the transplantation is to restore the hypoplasia in the bone marrow caused by chemotherapy and rebuild the weakened immune system (12). HSC transplantations have proven to be successful in various cases of leukemia/blood related cancers, and the various types of transplantations are used in different clinical settings. Allogeneic transplantation has been proven successful in treating patients with acute leukemia facing a relapse after the original chemotherapy treatment. Autologous transplantation is the ideal transplantation method

for those with chemotherapy-sensitive large-cell non-Hodgkin's lymphoma (13). An international scale trial conducted in 2009 comparing overall survival rates and relapse rates of ALL patients receiving allogeneic hematopoietic stem cell transplantation following chemotherapy; the three groups identified in the study included sibling-donor HSC transplantation, matched-unrelated-donor HSC transplantation, and a control of no additional treatment following chemotherapy. Across 267 patients, the overall survival (OS) for sibling HSC transplantation after 5 years was 44%, compared to 36% OS in unrelated donor transplantation, and 19% in chemotherapy. In addition to this, non-relapse survival rates after 5 years were significantly larger in both HSC transplantation groups compared to just chemotherapy, proving the success of this technique (14). A study published in 2013 examined the effect of different conditioning options for HSC transplantation, comparing myeloablative conditioning (MAC) with reduced intensity conditioning (RIC), and found that the MAC group had significantly higher toxicity scores (including mucositis, liver and gut toxicity) and longer average hospital stays. However, the relapse rate after 2 years in the RIC group was higher (36%) compared to 17% in the MAC group: it is important to note that the difference in relapse rates was non-significant, and the results of the study could suggest that despite RIC acting as a good potential substitute for MAC in older/frail patients, it could have a potential higher risk of relapse (15). This study proves the importance of not only determining the ideal transplantation type and conditions, but also ensuring the conditioning treatment beforehand is uniquely designed for each patient to optimize remission rates and decrease risk of relapse/graft-versus-host disease (GVHD).

Induced Pluripotent Stem Cells (iPSCs)

iPSCs were first developed by Shinya Yamanaka and team in Japan in 2006, and it revolutionized stem cell research. iPSCs are somatic cells (usually skin or blood cells) that were reprogrammed back into a pluripotent state to mimic ESCs (Figure 2). Unlike adult cells, iPSCs can differentiate into any cell type in the human body and have been used to develop neurons, gamete precursor cells, blood cells, liver cells, and more for the treatment of various diseases, including amyotrophic lateral sclerosis (ALS), Rett syndrome, Lesch-Nyhan syndrome, and Duchenne muscular dystrophy (16). A major area of research is how iPSCs can be genetically modified using the clustered regularly interspaced palindromic repeats and Cas9 (CRISPR-Cas9) system, along with zinc-finger nuclease (ZFN) and transcription activator-like effector nucleases (TALENs) for disease modeling. Wild type iPSCs can be modified to introduce the disease-causing gene and act as a control against mutation-removed patient iPSCs (17). An ongoing challenge in this application of CRISPR is the possibility of unintentional mutations as a result of the genetic modification (18). Engineered iPSCs have also been used to identify cancer-associated cellular mutations. One such mutation occurs in the promoter of human telomerase (or TERT)

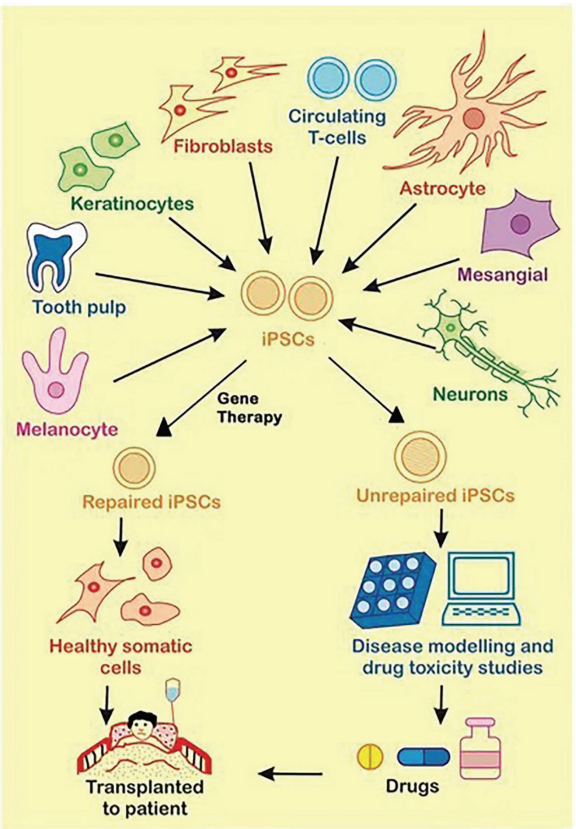

Figure 2. Overview of iPSC Reprogramming and Differentiation, adapted from Singh *et al.* (22). Induced pluripotent stem cells (iPSCs) are a laboratory-generated form of stem cells created as an alternative to embryonic stem cells (ESCs). iPSCs begin as somatic cells that are reprogrammed using the Yamanaka factors into a pluripotent state. The figure depicts the various sources from which iPSCs can be generated, including T-cells, neurons, fibroblasts, and more. From there, the iPSCs are able to differentiate into multiple stem cell types, and used in stem cell transplantation or for disease modeling purposes.

and engineering these mutations allowed scientists to discover that cells couldn't silence TERT transcription during cellular differentiation, and understand how this mutation works during tumorigenesis (19).

iPSCs can be used to differentiate into immune cells such as natural killer (NK) or T-cells in order to target cancer cells. iPSC derived NK cells can be genetically modified to optimize their cytotoxic activity and used as a cell therapy, and iPSC derived T-cells can be modified with chimeric antigen receptors (CARs) to recognize cancerous antigens and destroy them. iPSCs can also be engineered to produce certain molecules or microRNAs to induce apoptosis in the surrounding cancer cells (20).

Currently, studies have not yet examined how iPSC-derived HSC transplantation can be used in leukemia patients through clinical trials. However, pre-clinical trials have assessed how iPSC-derived HSC cells can be transplanted in immunodeficient mice to understand how long-term HSC transplantation can be applied in clinical settings using iPSCs as a precursor. A study published in 2024 induced mesoderm from the iPSC cells, and then transitioned into hemogenic endothelium, which was marked by the production of bone morphogenetic protein 4 and vascular endothelial growth factor (VEGF). The cells were then transitioned into hematopoietic stem cells through the removal of VEGF, and the transition was marked by the production of CD34+ blood cells. The blood cells were injected into immune-deficient mice, and the results concluded that around 25–50% of the human bone marrow cells were successfully produced post-engraftment in the mice, and half of the mice had 70% human bone marrow cells produced as a result of the engraftment after 16 weeks. This study provides a basis for how HSCs can be generated for clinical practices and stem cell therapy treatments in the future (21).

APPLICATIONS OF GENETICALLY MODIFIED HSCS FOR TREATING LEUKEMIA

Several studies have examined how HSCs can be modified for the purpose of CAR T-cell therapy, suicide gene systems, and dual engineered CAR-NK cell systems, which are explored below.

CAR T-Cell Therapy

HSCs are engineered with genes that code for chimeric antigen receptors (CARs) or T cell receptors (TCRs). CARs are synthetic receptors that allow T-cells to recognize extracellular antigens, in this case tumor-associated antigens, through a major histocompatibility complex-independent manner (23). CAR T-cells targeting the pan–B-cell marker CD19 were the first genetically modified stem cells treatment to be approved by the FDA (24). In 2018, a study was conducted to test the effectiveness of anti-CD19 CAR T-cells, a treatment used against aggressive B-cell lymphomas. Previous research has shown this therapy had high effectiveness among those who were resistant to chemotherapy or had a relapse within a year of stem cell transplantation. Anti-CD19 CAR T-cell therapy involves removing T-cells from the patient, genetically modifying them to express anti-CD19 CARs, and then injecting them back into the patient (25). CD-19 CARs are a cell surface molecule on B-cells and malignant B-cells (26). Patients with diffuse large B-cell lymphomas, or primary mediastinal B-cell lymphoma were treated. The treatment first involves leukapheresis, or extraction of white blood cells (27), and then axi-cel manufacturing. After this, the patients received low-dose preliminary chemotherapy from the drugs fludarabine and cyclophosphamide, and then were injected with CAR T-cells. The scientists assessed the effectiveness of the treatment by looking at the rate of objective response, along with the duration of the response, progression-free survival, overall survival, frequency of adverse effects, and the concentration of CAR T-cells and serum cytokines (chemical messengers involved in signaling within the immune system) in the blood. They found that genetic modification of the HSCs did not impact their differentiation and proliferation. The modified HSCs differentiated into myeloid cells and natural killer (NK) cells that successfully produced the intended CARs, and were able to correctly target the malignant CD19 B-cells. In addition to this, they found that the transduction of anti-CD28 CARs into HSCs combined with the anti CD19 CARs (CD19RCD28) had an enhanced cytotoxic effect. This test was repeated in *in vivo* mice models, and the CD19RCD28 group had the highest survival rate, proving the feasibility and effectiveness of this technique both *in vitro* and *in vivo* (28).

CAR-Modified NK Cells

A study published in Nature examined the impact of CAR-modified natural killer (NK) cells against acute myeloid leukemia (AML). The effectiveness of NK cells for targeting tumors is inhibited by the interaction between human leukocyte antigen (HLA)-E (found on the leukemic cells) and the inhibition receptor NKG2A. To overcome this challenge, the scientists modified the

CD33 CAR-NK cells by disrupting the production of the NKG2A inhibition receptor by editing the encoding gene, KLRC1, using the CRISPR-Cas9 complex. CD19-targeting CAR-natural killer (NK) cells are similar to the previously discussed CD-19 CARs and have a similar efficiency, however for this study, the scientists focused on targeting the CD33 antigen, as it is expressed in 88% of AML patients. NK cells were chosen because they have less side effects, a shorter lifespan than T-cells, and are able to kill cells CAR-independently.

Previous preclinical studies have proved the effectiveness of CAR33-NK cells in targeting CD33+ AML cells in a xenograft model *in vivo*, however the rate of antileukemic activity was inhibited by the immune mediated response of the tumor's environment. To overcome this obstacle, the scientists conducted transduction of NK cells from blood samples CAR targeting CD33 with a 30-70% rate of expression.

There were a total of four groups; non-transduced NK cells as the control, NK cells with reduced KLRC1 expression, unmodified CAR33-NK cells, and CAR33-NK cells with reduced KLRC1 expression (the main tested variable). This was done to study the impact of the individual components (CAR cells and reduced KLRC1 expression and the synergistic effect. After this, they knocked out the KLRC1 gene in both NK cells and CAR33-NK cells and found there was a 50% decreased amount of NKG2A-positive cells in the experimental group and therefore a significant decrease in the cell surface expression of NKG2A. The dual engineered NK cells had the highest tumor degradation capacity compared to the other three groups, and this effect was most significantly observed against AML cells expressing HLA-E. This NK cell group maintained the anti-tumor activity despite prolonged exposure to AML. These four groups were tested *in vivo* in a mice AML model as well, and the scientists found that the CAR33-NK with reduced KLRC1 expression group also had the most significant anti-mestastic effect and the mice in this group had the highest survival rate as well. Overall, this study was able to prove the effectiveness of dual engineered NK cell treatments as a promising treatment option to be explored in future clinical trials and studies (29).

HSC Modification for Suicide Gene Systems

A study examined how HSCs could be modified to produce both anti-CD19 CAR and a truncated epidermal growth factor receptor (EGFRt) to create a suicide gene system. The EGFRt acted as a safety switch and would initiate the suicide reaction in the presence of the cancer drug cetuximab. The purpose of this study was to determine whether this system would be an effective mediator of CAR gene therapy by eliminating the genetically modified cells post-transplant if there was a clinical need to do so, such as an adverse effect. The researchers used lentiviral vectors to hold the anti-CD19 specific CAR and EGFRt, and transducted human CD34+ hematopoietic stem/progenitor cells (HSPCs) with the vector. After evaluating the viability of the transduced cells, the scientists injected the cells into the mice model to evaluate the progression of human HSC growth and anti-CD19 CAR/EGFRt expression *in vivo*.

Cetuximab was administered to mice, with or without NK cells, to evaluate the suicide mechanism via antibody-dependent cell-mediated cytotoxicity (ADCC). Using flow cytometry and quantitative PCR to monitor cell growth and progression, and PET imaging with radiolabeled cetuximab to track EGFRt cells, the scientists determined the effectiveness of this system. Introduction of the anti-CD19 CAR and EGFRt genes did not affect HSC growth or proliferation *in vitro* or *in vivo*. The modified HSPCs engrafted in the mice successfully and produced various human blood types, proving that the genetic modification did not have an impact on hematopoiesis. In addition to this, they found that CAR expression acted as effective tumor control in mice affected with CD19 myeloid leukemia; CAR treatment potency was not affected.

Finally, the cetuximab/EGFRt suicide system was able eliminate 70–80% of EGFRt+ cells in the bone marrow/spleen over the 12 day period through the ADCC mechanism. Cell death was specific and did not affect non-targeted cells, confirmed using flow cytometry, positron emission tomography (PET) imaging, and quantitative polymerase chain reaction (qPCR), proving the tested genetic modification was significantly effective as a safety switch in cancer treatments (30).

LEUKEMIC STEM CELLS AND RELAPSE

Recent studies have found that stem cells can play a significant role in detection of leukemia in addition to treatment. Leukemic stem cells (LSCs) are a subset of leukemia cells that have the ability to self-renew and are resistant to conventional drugs and chemotherapy, displaying similar properties to those of hematopoietic stem cells. LSCs are thought to be the main cause of relapse after initial treatment, so identifying and eliminating these cells is crucial to preventing relapse

(31). Several markers are associated with LSCs, including CD34+, CD38+, CD25, CD71, CD123, HLA-, and CLL-1, which can be useful as prognostic biomarkers, or even targeting during cancer therapy treatments (32).

As previously noted, leukemic stem cells have associated biomarkers that show promise as the target of cancer therapies, and studies conducted using animal models have shown that targeting the CD123+ biomarker has been promising in eliminating AML LSCs. A recent study published in Natural Medicine attempted to use autologous anti-CD123 CAR T-cells in 12 adults facing relapsed/refractory AML. They were able to successfully manufacture the cells in 90.4% of the runs, proving the feasibility of the autologous genetic modification, however the efficacy of the intervention was hindered as cytokine release syndrome (CRS) was observed in 10/12 patients. 3 of the patients had a clinical response (blast reduction or disease improvement). The scientists found that myeloid-supporting cytokines were secreted during CAR T-cell therapy that actually supported the survival of the AML blasts and caused CAR T-cell exhaustion, so while the approach of targeting the CD123+ receptor seems promising, current studies have been unable to cross this barrier to investigate how anti-CD123 CAR T-cells could impact relapse and tumor development (33).

Another target of LSC elimination is inhibiting the signaling pathway for transcription complex NF-κB. This signaling pathway is crucial for proliferation and survival of LSCs, which is why research has been conducted in targeting this pathway using inhibitors such as Bortezomib. Several studies suggest that identifying how these biomarkers can be targeted can develop the world of bioengineered stem cells as a suicide gene delivering mechanism to eliminate LSCs (32).

The genetic modification of HSCs is an emerging solution to eliminate LSCs and can advance the field of cancer treatments. This can be done through techniques previously explored in the article, including CAR T-cell therapy in conjunction with a suicide gene system. More research is needed to understand what biomarkers can be used to target LSCs and how these biomarkers can be targeted effectively, however studies such as one conducted by Lagadinou *et al* provide a foundation for this kind of research. This study exhibited three key findings; first, that the most common type of LSCs are those with low levels of reactive oxygen species, known as ROS-low; second, that these LSCs overexpress the apoptosis-related protein BCL-2; and third, that inhibiting the production of BCL-2 could reduce oxidative phosphorylation, and in turn, help eliminate LSCs (34).

CONCLUSION

Stem cell therapy is an emerging field in the world of cancer treatment, and this review highlights the significance of such treatments especially for AML, and other forms of leukemia. The combination of this technology along with genetic engineering techniques shows promise for tumor reduction, especially through CAR T-cell therapy and the suicide gene system. Genetically modified stem cells can be used to increase the effectiveness of stem cell therapy by introducing or removing genes to control differentiation, protein production, and cell life. An application of this is to genetically modify stem cells to increase the chance of engrafted cell survival. An issue with many grafted cells is the low chance of survival, however stem cells can be modified to reduce apoptosis or inflammatory injury, therefore reducing the number of cells that die after transplantation. GMSCs can also be used for protein delivery to neighboring cells and reduce the risk of graft versus host disease (35).

CAR T-cell therapy is a major field of study within GMSCs, but while it has been proven to be extremely effective in reducing tumor progression, there are several associated potential side effects. This includes infections, an extreme reduction in antibody-producing B cells, cytokine release syndrome (CRS), and neurological issues grouped under the immune effector cell–associated neurotoxicity syndrome (ICANS). Symptoms of ICANS include confusion, excessive sleepiness, and impaired speech (36). During CRS, the injected T-cells can create an overproduction of cytokines, which can result in an extremely high fever and drop in blood pressure, and in rare cases, can become fatal. Beyond these symptoms, CRS can support the survival of AML blasts through kinase signaling, and eventually lead to CAR T-cell exhaustion (33).

All in all, genetically modified stem cell therapies have the potential to effectively target leukemia, however inflammatory side effects and issues from the CAR T-cell therapy can become counterproductive and decrease anticancer efficacy. A focus of future research should be to apply CAR T-cell therapy specifically targeting the CD123+ receptor (found predominantly in LSCs), used in conjunction with cytokine signaling inhibitors. The efficacy of a previously mentioned clinical study targeting this receptor was inhibited due to observation

of CRS; future studies can expand on this by using tocilizumab (Actemra) to manage CRS, as this drug blocks the activity of the prominent cytokine involved in immune responses (IL-6) (33, 36). This can help prevent undetectable relapse from occurring in AML patients. In addition to this, advancements in prognosis and early diagnostics specifically by targeting LSC associated biomarkers would enable us to attain better outcomes with regard to disease reduction.

A main focus of future studies should be to apply genetic modification to other stem cell types. There is a predominant focus on how this technique can be used for treatment in leukemia and a lack of research and understanding of how this can be applied to other cancers from a treatment perspective.

Leukemia generally affects the bone marrow, however similar cancer types such as Non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, and myelodysplastic syndromes (MDS), all of which are blood cancers, should be the focus of future studies (37).

ACKNOWLEDGEMENTS

The author acknowledges the support of Poonam Agarwal for reviewing the article and providing feedback on the writing.

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest regarding the publication of this article.

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