Stem Cells and Cloning: Advances and Applications

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REVIEW

Role of Stem-Cell Transplantation in Leukemia Treatment

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Abstract: Stem cells (SCs) play a major role in advanced fields of regenerative medicine and other research areas. They are involved in the regeneration of damaged tissue or cells, due to their self-renewal characteristics. Tissue or cells can be damaged through a variety of diseases, including hematologic and nonhematologic malignancies. In regard to this, stem-cell transplantation is a cellular therapeutic approach to restore those impaired cells, tissue, or organs. SCs have a therapeutic potential in the application of stem-cell transplantation. Research has been focused mainly on the application of hematopoietic SCs for transplantation. Cord blood cells and human leukocyte antigen–haploidentical donors are considered optional sources of hematopoietic stem–cell transplantation. On the other hand, pluripotent embryonic SCs and induced pluripotent SCs hold promise for advancement of stem-cell transplantation. In addition, nonhematopoietic mesenchymal SCs play their own significant role as a functional bone-marrow niche and in the management of graft-vs-host disease effects during the posttransplantation process. In this review, the role of different types of SCs is presented with regard to their application in SC transplantation. In addition to this, the therapeutic value of autologous and allogeneic hematopoietic stem–cell transplantation is assessed with respect to different types of leukemia. Highly advanced and progressive scientific research has focused on the application of stem-cell transplantation on specific leukemia types. We evaluated and compared the therapeutic potential of SC transplantation with various forms of leukemia. This review aimed to focus on the application of SCs in the treatment of leukemia.

Keywords: stem cell, leukemia, transplantation

Introduction

Stem cells (SCs) are undifferentiated cells that can be differentiated into other types of cell andalso have the potential to proliferate and self-renew to producenew SCs. In mammals, there are two broad type of SC. Embryonic SCs (ESCs) are present in the early life of the embryo and isolated from the inner cell massor morula of the blastocyst (future germ layer, such as endoderm, ectoderm, or mesoderm of the embryo).[1–4] The surrounding section of the morula is known as the trophoblast, which can develop to the future placenta. Adult SCs (ASCs) are found in various tissue types of developed mammals.[5] ASCs are useful for tissue regeneration and repair after severe injuries.[1,6]

SC populations may behave abnormally or be altered by genetic or environmental factor, resulting in the development of cancer. Leukemia comprises a group of hematologic disorders that usually begin in the bone marrow and resultin a high number of abnormal blood cells. It is the result of deregulation of normal

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hematopoietic SC (HSC) development by genetic mutation that produces a cell population known as leukemic SCs (LSCs). The generation of blood cells depends on the regulation of differentiation and proliferation characteristics of HSCs.[7] Deregulated differentiation and proliferation activity of HSCs, including chromosomal translocation and somatic mutation, leads to different hematologic disorders. There are four major abnormalities identified under LSCs: such as acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL),[8] chronic LL (CLL) and chronic ML (CML).[4] Leukemia and lymphoma (Hodgkin's lymphoma [HL] and non-HL [NHL]) are the two major types of blood cancers that result from uncontrolled proliferation of white blood cells, and were the first to be treated clinically using HSC transplantation (HSCT).[1,–9-11] In addition, HSCT is used as a therapeutic option for many nonhematopoietic malignancies, aplastic anemia, and certain inherited disorders like severe thalassemia, sickle-cell disease, and other inherited metabolic disorders. Historically, HSCs were obtained only from bone marrow, but are now mostly harvested from peripheral blood after mobilization through administration of hemaTtopoietic growth factor and from the umbilical cord blood (UCB) of newborns.[4,9]

SC-based therapies become the major concern of researchers after the first effective bone-marrow transplant in 1968.[12] Globally, food and drug administrations design regulations on the application of SC therapies. An increase in scientific knowledge of cell-differentiation pathways has promoted the application of SC therapy.[12] Since the application of SC therapy emerged as a new insight into cellular therapeutic potential, food and drug administrations have continuously driven awareness and designed regulation with regard to SC therapies. SCs serve as a novel cellular therapeutic approach in the field of regenerative medicine to treat various disorders.[13] In addition to renewing and proliferating themselves, they are capable of differentiation to specialized functional cells.[14] This enables them to substitute various injured cells, such as cardiomyocytes, fibroblasts, and endothelial cells.[15] In addition, regenerative medicine has significant therapeutic potential through the application of SCT to restore impaired blood cells.[16]

HSCT has broad application in treating different malignant and nonmalignant hematologic disorders. Researchers have noted that >40,000 HSCTs are performed every year to treat these disorders.[17] In this context, autologous SCT (auto-SCT) and allogeneic SCT (allo-SCT) are the best known and most applicable.[18] There are SC types that have the capability of being the source for SCTs. Bone-marrow SCs are the major sources for treating hematologic and nonhematologic disorders.[19] Similarly, peripheral blood $CD34^{+}$ cell have hematopoiesis potential for HSCT.[20] With respect to recent scientific advancement,HSCs are generated from pluripotent ESCs that require the transition state from endothelial to hematopoietic progenitor cells to resolve HLA-mismatched problem.[21] The recent investigation done by Serap et al (2019) and his colleagues hypothesized that achievement of effective HSCT may also associate with non-hematopoietic progenitor cells, very small embryonic-like SCs (VSELSCs).[22] They differentiate into HSCs in vitro.[23] With specific forward reprogramming protocols, induced pluripotent SCs (iPSCs) have therapeutic potential to generate hemato-endothelial progenitor (HEP) cells.

Co-administration of chemotherapy along with auto-SCT leads to a decrease in the level of regulatory T-cells. In response to the dysregulated immune system, biological characteristics of mesenchymal SCs (MSCs) contribute to hematopoietic reconstitution and an efficient HSC engraftment.[24,25] On the other hand, bone marrow derived MSCs are other components of hematopoietic niche.[26] Therefore, this review assessed different types of SCs that are utilized as the source and as support of SC transplantation. In addition, we also summarized the role of allogeneic and auto-SCT in the treatment of various types of leukemia.

Generation of Hematopoietic Stem Cells from Human Embryonic Stem Cells

The involvement of ESCs is the new therapeutic insights having a regenerative potential to restore impaired tissue or cells.[27] ESCs are the source of SCs for cellular transplantation therapies; however, they may also lead to uncontrolled cell proliferation which also results in the development of cancers.[28] The challenges of using these cells are their characteristic features of chromosomal abnormality and mutation during in vitro.[29] Regard to this, c-MYC oncogene may be expressed that results in cancer cells than their cellular therapeutic significant.[29] They require a safety concern due to their teratoma formation.[30] Although they have teratoma effect, ESCs have a significant role in the transplantation process.[28] Human ESCs (hESCs) serve as the source of development of cellular lineages through signaling pathways.[13] Recently, protocols have been on the way to be designed to generate HSCs from pluripotent ESCs in vitro. The generation

of HSCs from those pluripotent ESCs requires a transition from endothelial to hematopoietic progenitor cells to resolve HLAmismatching.[21] The hematopoietic transcription factor Runx1 promotes the commitment of hematopoietic cellular lineages by activating the expression of Runx1a. NOTCH signaling enhances the transition state, while the TGFβ-signaling pathway inhibit it.[31] Recently, generation of HSCs was achieved by Wang et al from hESCs andhumaniPSCs (Figure 1). The commitment stages that had been examined by those scientists confirmed the synthesis of hematopoietic cells from hESCs.[32] In support of this, recently the ESC gene *SLL4*was identified and used as a therapeutic target for leukemia. Because of its importance in the ESC fate, *SALL4* expression need to be reactivated during the reprogramming process of mouse embryonic fibroblasts to be converted into iPSCs. Under normal condition, *SALL4* is expressed highly in $CD34^{+}CD38^{-}$ HSCs and llittle in $CD34^{+}CD38^{+}$ hematopoietic progenitor cells. Therefore, the main application behind this ESC gene product is as key player in hematopoietic differentiation. Consequently, downregulation of this gene could be considered a therapeutic option for leukemia.[33]

Generation of Hematopoietic Progenitor Cells from Induced Pluripotent Stem Cells

iPSCs were introduced as an alternative SC-based therapy method in 2006, by Takahashi and Yamanaka.[34] Reprogramming of SCs through the integration of viruses with these cells induces differentiation capability in various tissue types.[35] These are pSCs, which are generated from adult somatic cells through in vitro experimental investigation.[36] They are synthesized in vitro by reprogramming mature mouse fibroblast cells through epigenetic modification.[34] In human beings, production of iPSCs was started through the introduction of four genes — *SOX2*, *MYC*, *OCT4*, and *KLF4* — into matured somatic fibroblasts[37] and other human somatic cells.[38] The genes are induced in these cells through the encoded retrovirus.[39]

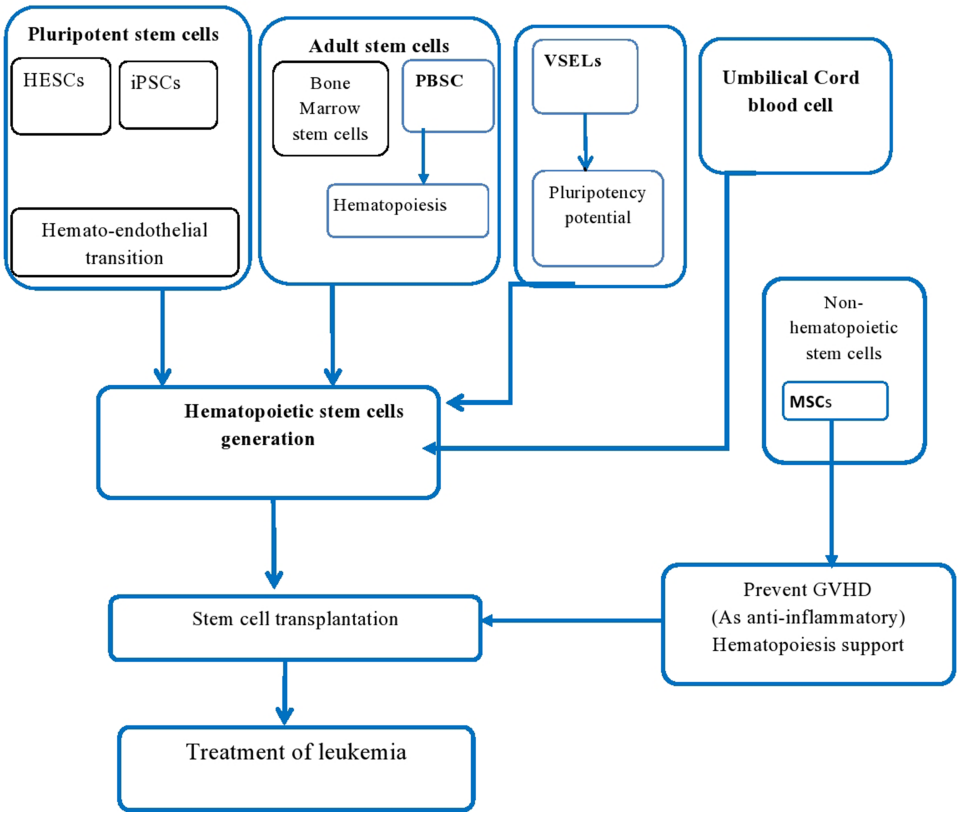

Figure 1 Role of different types of SCs in SC transplantation. MSCs were the nonhematopoietic source utilized to reduce GVHD (reduce risk of graft failure by secreting soluble factors with anti-inflammatory properties), efficient HSCs support to engraftment of transplant, hematologic reconstitution, and to improve the HSCT outcome. HSCs can be generated from the hematoendothelial transition process from HESCs to HiPSCs, and commonly from bone-marrow SCs, PBSCs, and umbilical cord blood. The pluripotent potential of VSELSCs also enables to generate HSCs.

Abbreviations: GVHD, graft-vs-host disease; HESCs, human embryonic SCs; HSCs, hematopoietic SCs; HSCT, hematopoietic SC transplantation; HiPSCs, human induced pluripotent SCs; MSCs, mesenchymal SCs; PBSC, peripheral blood SC; VSELSCs, very small embryonic-like SCs.

The ability of iPSCs to expand into multicellular lineages enables them to be a potential SC-therapy method. Various types of patient-specific SCs have been synthesized from their expansion process in vitro.[40] Research has revealed their cellular therapeutic significance in various hematologic malignancies, such as CML, MDS, AML,[22] and BCR-ABL− myeloproliferative neoplasms.[41] Donor blood cells are reprogrammed to iPSCs to generate patient-specific SCs.[40] With specific forward-reprogramming protocols, iPSCs have the therapeutic potential to generate hematoendothelial progenitor cells. Lange et al demonstrate the possible generation of hematopoietic progenitor cells by combinatorial expression of transcription factors SCL, LMO2, GATA2, and ETV2[42] (Figure 1). Moreover, researchers have been trying to generate hematopoietic progenitor cells from PSCs. Shan et al described possible strategies for generation of HSCs from human mesenchymal cells with hematopoietic potential (Figure 1). They revealed the derivation or generation of hematopoietic progenitor cells from mouse PSCs using in vitro induction methods. Therefore, iPSCs can be have possible therapeutic potential in SCT; however, they present safety concerns, due to their teratoma formation.[30] Allogeneic transplantation of bone marrow or umbilical cord reveals rejection, due to the effect of graft-vs-host disease (GVHD) and disease relapse, which restricts its applicability. In cases of auto-
HSCT, there is no risk of rejection, but there remain leukemic cells that induce disease relapse. Collectively, these disadvantages of bone-marrow HSCT mandate alternative sources of HSCs aiming to reduce GVHD, disease relapse, and bone marrow–failure syndrome. Considering this, iPSCs represent a suitable source to generate HSCs in vitro with limited immunogenicity.[43] These have a major advantage over bone-marrow and cord types, since their autologous transplantation from iPSCs does not induce GVHD.[44]

Very Small Embryonic-Like Stem Cells

Bhartiya et al characterized VSELSCs as the "true SCs" and the subset of different SC population, such as HSCs, ovarian SCs and MSCs. They express the OCT4A antigenic marker in their nucleus.[30] The pluripotency features of VSELSCs enhance their expansion in vitro using the pyrimidoindole-derivative molecule UM171,[45] and in turn are utilized for expansion of $CD34^+$ HSCs.[46] VSELSCs are involved in homeostatic processes, because they are found in quiescent stage, and later they differentiate into ASCs. They differentiate into HSCs in vitro.[23] VSELSCs can be generated from primordial germ cells and undergo further differentiation into HSCs[47] (Figure 1). Bone marrow–derived VSELSCs may not have features characteristic of hematopoietic progenitor SCs, but they can retain hematopoietic features through external-stress growth factors.[48] The transcriptional factors Oct4A), Nanog, and Rex1 are found in VSELSCs, but they are not expressed in HSCs.[22] Treatment of immunocompromised ALL[8] patients with granulocyte colony–stimulating factorincreases mobilization of VSELSCs to the peripheral circulation.[49] Dissemination of VSELSCs to the circulation promotes the regeneration of tissue.[49] A recent investigation done by Serap et al hypothesized that achievement of effectiveHSCT may be associated with nonhematopoietic progenitor cells — VSELSCs.[22] The expression of transcription factors and pluripotent markers may contribute to their therapeutic potential in SC transplantation. Demonstrations on immunocompromised mice have shown that VSELSCs have a lower teratoma effect.[47] Similarly, an investigation done on animal models showed that they have the capability to differentiate into HSCs.[46]

Potential Effect of Cotransplantation of Mesenchymal Stem Cells to Treat Leukemia

Bone marrow–derived MSCs are important to regenerate injured tissue.[50] Recently, MSCs have served as a new cellular therapy method in the field of regenerative medicine.[13] They inhibit cancer-cell proliferation through secretion and inhibition of Dkk1- and Wnt-signaling pathways, respectively.[51] Besides this, MSCs alter the immune system to regenerate damaged tissue and decrease inflammation.[52] GVHD is one of the complications of both auto-SCT and allo-SCT during treatment.[53] This posttransplantation complication is associated with immunologic intolerance.[53] Indeed, MSCs have been shown to support the engraftment of autologously or allogeneically transplanted HSCs by secreting soluble factors or immunomodulators, such as $TGF\beta_1$ and HGF which inhibit the proliferation of $CD4^+$ T_H1, T_H17, $CD8^+$ T, and natural-killer cells, leading to prevention of GVHD.[6,24,26] Therefore, GVHD that occurs after HSCT can be treated by coinfusion with MSCs.[54] Bone marrow–derived MSCs are components of the hematopoietic niche. Additionally, they have the capability to regulate the hematopoiesis process through interactionand communicating with HSCs and progenitor cells[55] (Figure 1).

Umbilical Cord Blood Cells and Haploidentical Transplantation

Donor availability is a very important issue, particularly in patients from ethnic minorities. A haploidentical donor and CB allow allo-HSCT in the majority of transplant-eligible patients.UCB is a well-established cellular product source for hematopoietic reconstitution and transplantation.[37] It is derived from fetal tissue and acts as a potential source of progenitor SCs to synthesize matured HSCs[16] (Figure 1). The lower complication rate of GVHD and less stringent HLA-matching requirements make it a valuable source of HSCs.[56] It is more highly enriched with HSCs/progenitor cells than peripheral blood with regard to colony-forming unitgranulocyte/macrophage progenitors and $CD34^+$-cell content.[57]

The effect of HLA mismatching is less severe in mismatched UCB transplantation than unrelated peripheral and bone marrow–blood transplantation;[58] therefore, higher numbers of mismatched donors may donate to save lives. Compatibility at the DRB1-allele and HLA-A and -B antigen level is better for UCB transplantation to be selected traditionally without consideration of HLA-C.[59] UCB has significance for allo-HSCT transplantation, because it requires lower HLA matching than for unrelated donors.[59] In AML, unrelated CB transplantation has failed, due to nonrelapse mortality.[60] However, the cost of CB delaying engraftment and risk of infection are still challenges in its application for hematologic diseases, including leukemia.[61,62]

In cases of rapid requirement of allograft and absence of an HLA-matched donor, HLA-haploidentical SC transplantation is considered a therapeutic option.[63] Peripheral and bone-marrow SCs can be donated from these family members if they have one common haplotype.[64] HLA-haploidentical cells are considered an optional source for HSCT.[65] In haploidentical transplantation, the graft contains lower of T-cell content to diminish GVHD.[66] Outcomes of haploidentical HSCT may be affected by innate immune cells like T cells and natural-killer cells.[67] In high-risk acute leukemia, the applicabilion of HLA-haploidentical HSCT is elevated.[65] However, outcomes of nonrelapse mortality and GVHD may be increased from haploidentical HSCT with higher HLA mismatching including from partially related donors, as the content of T-cell is replete.[68]

Bone-Marrow Stem Cells as Source for Stem-Cell Transplantation

A soft, gelatinous tissue, bone marrow is used as the source of peripheral HSCs.[69] Researchers have argued that both bone marrow and peripheral blood are major sources of SCs. SCASCs generated from bone marrow are known as bone-marrow SCs,[37] having clinical significance in restoring damaged cardiac tissue through gene therapy.[70] Also, they can be a potential source for auto-HSCT..[37] There is an improvement in GVHD in patients with bone-marrow SC transplantation compared to peripheral blood SCs (PBSCs).[19] Bone marrow–SC transplantation is utilized in various hematologic malignancies, such as AML, ALL, and CML. The use of bone-marrow transplantation from compatible donors is the most effective treatment for CML.[71] Allogenic bone-marrow transplantation is an effective alternative treatment option for patients who are resistant to chemoradiation therapy and have a higher probability of relapse.[72] The physician removes marrow from the donor's hip bone using surgical procedures, including anesthesia, sterile needles, and syringes, and replaces the donated bone marrow within 4–6 weeks. As the level of T cell compare in both bone-marrow transplantation and PBSCs, the concentration of T cells is reduced in bone-marrow transplantation.[19]

Peripheral Blood Stem Cells as Source for Stem-Cell Transplantation

Recent SC-transplantation protocols state that mobilization of HSCs from bone marrow to peripheral blood is an effective treatment method in the majority of transplanted patients.[73] Although bone marrow is major source of SCs, a hematopoietic growth factor found in PBSCs showed that these are also another possible source of SCs.[74] PBSCs from bone marrow are a valuable source in restoring hematologic disorders.[69] The potential effect of PBSCs depends on hematopoietic development and enhancement of immunologic profiles, and hence they are a valuable source of HSCs to treat hematologic disorders. Peripheral blood $CD34^+$ cells have hematopoietic potential for SCT.[20] Javarappa et alpurified hematopoietic progenitor cells from $CD4^+$ peripheral blood cellsafter which the cells differentiated into megakaryocytes and myeloid-lineage cells[75] (Figure 1). PBSCs serve as a valuable SC source if mobilization is supported by granulocyte colony–stimulating factor.[19] They are applicable in autolo-SCT in the treatment of multiple myeloma.[76] The utilization of peripheral SCs as a source of SCs may induce the occurrence of GVHD.[77] Even if they have such effects, the immune system has been enhanced, due to elevation of T-cell secretion. On the contrary, the elevation of T cells may also cause GVHD development;[19]

however, PBSC collection in children may expose them to metabolic complications, including hypocalcemia and hypoglycemia.[78]

Hematopoietic Stem-Cell Abnormalities in Leukemia

The tight control in proliferation and differentiation of HSCs has significant value for the synthesis of blood cells.[7] Multipotent HSCs are responsible for cell division and proliferation.[79] Somatic mutation of T cells during DNA methylation and posttransplantation alteration are risk factors for ALL.[8,80] CML is a hematologic disorder induced by reverse chromosomal translocation on t(9;22)(q34;q11)[81] and *BCR–ABL* oncogene effects on proliferative myelogenous cells.[82] Mutated gene *BCR–ABL*, has a tyrosine-kinase effect and induces the release of highly proliferative myelogenous cells from bone marrow.[81] The *MYC* gene is another oncogene that induces gene expression and has a proliferative effect on hematopoietic progenitor cells.[83] In addition to this gene, *BCL2* is another mutated gene that inhibits programmed cell death. As such, cancerous cells proceed with their continued proliferation and leukemic cells are released from the tissue where they were generated.[84] Hitzler et al reported that a mutation of the *GATA1* gene in acute megakaryoblastic leukemia affects hematopoietic transcriptional factor. On the other hand, chromosomal translocation of t(7;11)(p15;p15) HSCs lead to the integration of genes, including *HOXA9* and *NUP98*, which also leads to distortion in the transcriptional process of hematopoietic precursor cells.[85] Aberration of the transcriptional process in these cells induces abnormal cell proliferation, which may lead to AML.[85] Overproliferation of lymphoblasts within bone marrow can also result in the pathogenesis of ALL.[8,49]

Hematopoietic Stem-Cell Transplantation to Treat Leukemia

Emphasis on the eradication of hematologic malignancies has shifted from cytotoxic chemotherapy to donors' immune cells.[86] HSCT is utilized by 20,000 people in the US every year.[87] It is applicable in treating patients with rare diseases, such as AML,[22] ALL,[8] CML, Burkitt's lymphoma, HL, and NHL,[11] and other hematologic malignancies.[88] Although it serves as an alternative treatment method, HSCT still has a relapse risk among 40%–80% of recipients.[89] Both auto-HSCT and allo-HSCTare the main alternative cellular therapeutic methods to treat leukemia. Auto-HSCT is the appropriate and applicable therapeutic option for multiple myeloma[1,18] and HL.[11] Charles et al explained that auto-HSCT was more frequently utilized by European and North American countries than allo-HSCT to treat myeloma. A lower mortality rate for myeloma is seen with auto-HSCT. Auto-HSCT is an established treatment approach if myeloma is at an acute stage, but for older patients it requires extra improvement.[90] The occurrence of GVHD among myeloma patients who undergo allo-HSCT is 50% compared to 5%–20% of occurrence of auto-SCT patients[91] (Figure 2). As such, fewer GVHD effects have been seen in auto-SCT n treating multiple myeloma and HL.[11] Furthermore, in HIV-related lymphoma, auto-HSCT is considered an applicable therapeutic option in both relapsed HL[1] and relapsed NHL patients.[18,92]

On the other hand, allo-HSCT is a curative treatment approach for severe AML[93] It has been confirmed that hematologic toxicity is lower in these recipient patients. Allo-HSCT has also been used as a treatment option for acute lymphoid leukemia and multiple myeloma.[1,23,94] Though alternative treatments remain undefined, it is a valuable treatment tool for hematologic malignancies. Reduced-intensity conditioning after allo-HSCT has been seen in Spain.[95] The toxic effect of allo-HSCT is associated with graft-vs-leukemia reactions. Chronic myelogenous leukemia patients show lower relapse rate than other allogeneically transplanted leukemia patients.[96] The therapeutic landscape of CML has shifted dramatically with developments tyrosine-kinase inhibitors (TKIs), which target the BCR–ABL1 hybrid oncoprotein and block the constitutive activity of tyrosine kinase. The course of CML is typically triphasic, with an early indolent chronic phase (CP), followed by an accelerated phase and a blast (crisis phase (BP).[97,98] For selection of appropriate TKIs, of CML patients should be tested for BCR–ABL1 kinase–domain mutation (mutation profile), disease phase, and patient comorbidities. For example, if the patient has such mutations as Y253H, E255K/V, or F359C, physicians recommend dasatinib or bosutinib as TKI. On the other hand, if patients are in an advanced disease phase (BP) or CML-CP (with T315I mutation), third-generation ponatinib is preferred over imatinib.[99–103] However, allo-HSCT remains a therapeutic option for patients in CML-CP whose CML has progressed after at least two TKIs and after trialing ponatinib therapy (for T315I mutation) to reduce the CML burden, and for the effectiveness of the transplantation.[99,100,102] An improvement in immunologic tolerance and lowered GVHD effect mean allo-HSCT is the only curative treatment option for

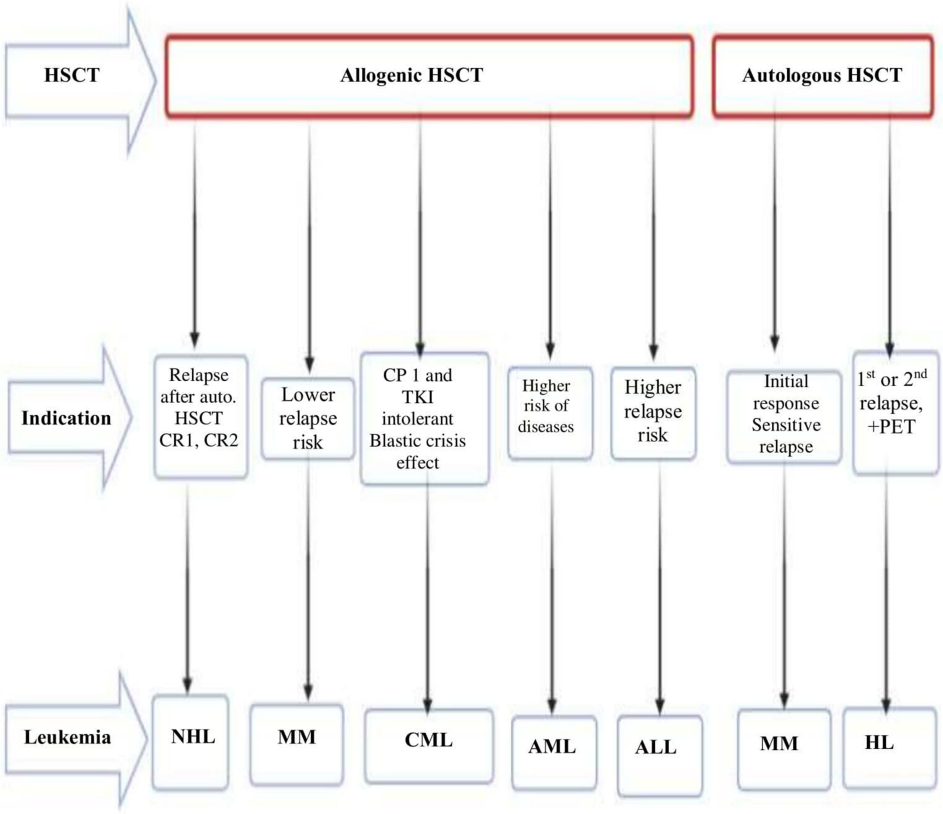

Figure 2 Comparison of allogeneic and autologous stem-cell transplantation with hematologic disorders. Autologous stem-cell transplantation has been utilized as a treatment protocol to treat MM and HL, due to its initial response, low relapse sensitivity, and positive positron-emission tomography (+PET). Patients at higher risk or progress of AML are treated with allo-HSCT. Chronic phase 1 (CP1), TKI intolerance, and blast crisis enables allo-HSCT to be a standard treatment option for the treatment of CML. Allo-HSCT is also a treatment option for NHL patients presenting with complete remission 1 and 2 (CR1 and CR2) indications and also relapse after auto-HSCT. Although they have graft-vs-leukemic toxic effects, they are a significant alternative cell-based therapy to treat hematologic malignancies.
Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukaemia; HL, Hodgkin's lymphoma; MM, multiple myeloma; NHL, non-HL.

CML-BP[104] (Figure 2). Similarly to CML, highly complicated and severe AML is effectively treated with allo-HSCT.[22] Complications of AML may lead to higher mortality and morbidity rates, which may be due to chronic GVHD among patients >50 years old.[105] Pediatric ALL patients presenting with indications of higher relapse risk are treated (10% of treatment) with allo-HSCT.[106]

ALL patients who develop high relapse risk are indications for treatment with allo-HSCT.[107] Allo-HSCT is a standard treatment method for ALL patients who are at higher risk.[108] The use of allo-HSCT has lower toxicity in young patients.[86] Allo-HSCT has lower relapse risk than auto-HSCT in multiple myeloma.[18] Graft-vs-tumor reactions in hematologic malignancies depend on the donor's T cells and donor lymphocyte infusions. The decision to perform allo-HSCT depends mainly on reduced intensity conditioning.[109] Researchers haverecommended that the use of allo-HSCT should depend on strong clinical data; however, 28%–49% of allo-HSCT patients develop relapse risks for disease.[110] Moreover, allo-HSCT has been widely applied as a therapeutic option in both HL and NHL.[11]

Conclusion

SCs play a major role in cell-based therapy to treat both hematologic and nonhematologic malignant disorders. They are mainly involved in the application of transplantation. Adult SCs (bone-marrow SCs), PBSCs, and UCB are the major potential sources of HSCs used during SC transplantation. Similarly, apart from ethical issues associated with disruption of inner cell mass, ESCs and ELSCs are also sources of HSCs as a therapeutic option to be utilized in SC transplantation. The generation of HSCs from iPSCs through hematopoietic–endothelial transition will be therapeutic options during times of inadequate availability of compatible donors. On the other hand, non-HSCs and MSCs are possible to use as coinfusion to support engraftment of transplants, hematologic reconstitution, and manage GVHD

posttransplantation. Auto-HSCT and allo-HSCT are the major cellular therapeutic options to treat leukemia. The lower relapse risk, blast crisis, TKI-intolerant patients in the CP and at higher risk of disease, and higher relapse risk are indications to utilize allo-HSCT rather than auto-HSCT to treat different types of leukemia. Likewise, primary refractory sensitivity to relapse and positive PET are basic indications to prefer auto-HSCT to allo-HSCT in treating both multiple myeloma and HL. Therefore, allo-HSCT is a more applicable standard cellular therapeutic option than auto-HSCT for many classes of leukemia.

Abbreviations

Allo-HSCT, allogeneic hematopoietic stem–cell transplantation; auto-HSCT, autologous HSCT; CML, chronic myeloid leukemia; GVHD, graft-versus-host disease; ESCs, embryonic SCs; iPSCs, induced pluripotent SCs;MSCs, mesenchymal SCs; PBSCs, peripheral blood SCsVSELSCs, very small embryonic-like SCs.

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Author Contributions

All authors made a significant contribution to the work reported, whether in conception, study design, execution, acquisition of data, analysis, interpretation, or all those areas; took part in drafting, revising, or critically reviewing the article; gave final approval to the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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