Journal of Experimental and Clinical Medicine
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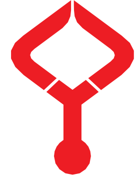

Review Article

J Exp Clin Med
2023; 40(1): 171-179
doi: 10.52142/omujecm.40.1.32

From laboratory studies to clinical applications mesenchymal stem cells in cancer treatment: Translational oncology

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Received: 11.08.2022 • **Accepted/Published Online:** 22.08.2022 • **Final Version:** 18.03.2023

Abstract

Stem cell-based studies have accelerated to treat various pathologies, particularly neurological, cardiovascular, orthopedic diseases and cancer with the understanding of their therapeutic potential after their discovery. Stem cells have recently aroused great interest as a promising treatment option in fighting to cancer with extensive study in the fields of cancer biology. Nevertheless, much uncertainty regarding the act of stem cells in cancer development and treatment remains obscure before the clinical use of stem cell investigation. Despite many obstacles, the migration ability of stem cells, the bioactive factors they secrete, and their immune regulatory properties make them advantageous for gene therapy strategies. However, unknowns and a lack of scientific data remain concerning the use of stem cell-based therapies. Therefore, more experimental data are needed to confirm the different study results presented by different scientific communities. In this review, we focused on summarizing the available experimental and clinical data on the potential uses of mesenchymal stem cells in cancer therapy.

Keywords: anti-tumoral activity, cellular therapy, cancer, mesenchymal stem cells

1. Introduction

Mesenchymal stem cells (MSCs) were defined 40 years ago by Friedenstein et al. as non-hematopoietic cells isolated from the bone marrow (1). MSCs, depending on their stem cell properties, which have the potential to renew themselves and differentiate into cells from the same or different embryonic layer, are easily accessible cells because they can be obtained from many adult tissues (2-7)

Although MSCs show different characteristics according to the tissue sources from which they are obtained, they are basically described by the International Cellular Therapy Association (ISCT) depending on several properties; including 1. adhesion to plastic surface when grown in vitro, 2. having no expression of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR but having high expression of CD73, CD90, and CD105, 3. differentiation to adipocytes, chondrocytes, and osteoblasts when cultured under certain conditions (8-10).

MSCs constitute a group of stem cells that are widely studied in clinical practice due to their ability to be cultured easily *in vitro*, their potential to differentiate into cells from different embryonic layers, their immunomodulatory properties, tissue repair, and their secretion of many paracrine factors (11).

MSCs can be induced into many different cell types of mesodermal and non-mesodermal origin (8). MSCs have significant therapeutic potential for stem cell transplantation, repair of damaged organs, and gene therapy because of their potential for self-renewal and multi-lineage differentiation, and they emerge as the most promising candidates in regenerative medicine and clinical therapy (12). Their low immunoreactivity and high immunosuppressive properties make MSCs an important source of cells for both autologous and allogeneic applications (13).

Until today, clinical applications have been encountered in the treatment of orthopedic fractures and osteoarthritis (14, 15), and in the treatment of cardiovascular diseases (16, 17). In addition, MSC-based studies as cellular therapeutics have been carried out for many diseases including neurological diseases (18, 19), liver regeneration (20), acute kidney injury (21), cardiac ischemia (22) and diabetes (23) in preclinical animal models. At the same time, ongoing preclinical studies propose that MSCs may be appropriate targets for cell therapy in many cancers. However, the antitumor potentials of MSCs are still unknown. In some of the studies targeting many types of cancer, MSCs were found to show protumorigenic effects (24-28), while in some others it was observed that they showed antitumorogenic effects (29-40).

It has been considered that the various findings showing stimulating or inhibiting results of MSCs on tumor growth may be related to change in tumor patterns, differences in MSC

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source, donor-dependent variables, dose or timing of MSC administration, cell isolation and culture method, number of stem cell passages used, and the other experimental conditions (25, 41). Therefore, more scientific data is needed to make these studies suitable for future clinical research. At the same time, it is important to standardize the studies and explain the underlying reasons for this variability in the data before the results obtained from laboratory studies are transferred to clinical applications.

2. The Sources of MSC and Their Role in Cancer Treatment

Despite significant successes in treatment, cancer is still one of the major causes of death worldwide. The nature of cancer, such as its aggressive nature and metastatic potential, as well as weakness in the host defense mechanism and failures in therapeutic management, may be important causes of treatment failure. In this respect, discovering the cellular mechanisms and signaling pathways that are effective in tumor formation and development will enable the development of new targeted anti-cancer therapies (35).

Understanding that MSCs migrate to damaged tissues and areas of inflammation has an important place in the emergence of their therapeutical aspect in the therapy of diseases. Various research has reported that MSCs can cause tumor growth inhibition or induction, depending on the types of tumor which MSCs contact and interact with (8, 42).

Studies have reported that MSCs originating from different tissues show different properties. According to the results of various phenotype and function studies, it has been reported that MSCs obtained from different tissues are not completely similar, but represent an extremely heterogeneous cell population that varies depending on various extrinsic and intrinsic factors (43). In a study comparing the therapeutical potentials of the MSC population obtained from different sources, they showed that MSCs gained similar phenotypic and functional properties after the first passes; however, bone marrow derived MSCs (BMMSCs) performed better than other sources for protection of tissue viability and has a paracrine effect. Although MSCs originating from different sources exhibit similar behavior in cell culture, they secrete different paracrine factors and exhibit different therapeutic potential (41). Accordingly, MSCs obtained depending on the tissue source are thought to show different anti-cancer properties. It has been shown that co-culture of human umbilical cord blood and adipose tissue-derived MSCs with primary glioblastoma multiforme cells revealed the inhibitory and apoptotic effect of umbilical cord-derived-MSCs (hUCMSC) on glioblastoma multiforme cell growth and caused apoptosis and the proliferative effect of adipose tissue-derived-MSCs (hATMSC) (44). In the experimental model investigating the therapeutic effect of ATMSCs on hepatocellular carcinoma, it was found that cancer cell proliferation decreased and also, the transcriptional expression of TIMP-1, -2 and -3 and TIMP-1 and -3 were significantly increased in HepG2 and PLC-PRF-5 cells, respectively. It has been reported that increased TIMP secretion may be a mechanism used by stem cells to restrict tumor invasion (45).

It was highlighted that hUCMSCs exhibited growth inhibition in xenograft models of human breast cancer cells and the same results were obtained after repeated experiments. In the study, it was observed that hUCMSC significantly inhibited DNA synthesis in breast cancer cells depending on the applied dose and the cells were arrested in the G2 phase. Accordingly, it has been suggested that hUCMSCs cause cell cycle arrest and cause growth inhibition of cancer cells (29).

There are studies showing that hUCMSCs induce apoptosis in cancer cells and inhibit the proliferation of tumor cells (46). Another research also reported that after 48 hours co-culture of hUCMSCs and Esophageal cancer cells (Eca109) resulted in significant upregulation of B-cell lymphoma 2 (Bcl-2), survivin, matrix metalloproteinase 2 (MMP-2) and matrix metalloproteinase 9 (MMP-9) expression levels according to controls (47). Besides, the study performed in rats suggested that hUCMSCs could be used as cellular therapy for breast cancer (34). The effect of MSCs on cancer proliferation varies according to the source obtained, cancer cell, application dose and duration, and application method. The studies from the literature were summarized in Table 1 according to MSC source, cancer model, and experimental protocol.

Table 1. Study summaries showing the effects of MSCs on cancer proliferation

MSCs source	Cancer model	Experimental protocol	Result	References
Human umbilical cord	Human breast cancer cell line	In vitro co-culture [1:6 (SC:CC)] and in vivo (xenograft model; 0.5×10^6 cells per injection)	Inhibition of the proliferation	(29)
Human umbilical cord	Human malignant glioma cell line	hUCMSCs and activated hUCMSCs (by interleukin-2, interleukin-15, granulocyte macrophage colony-stimulating factor); in vitro co-culture [0:1, 1:1, 5:1 and 10:1 (SC:CC)]	Inhibition of the proliferation	(48)
Human bone marrow, adipose tissue, and umbilical cord	Ovarian cancer cell lines	In vitro co-culture [1:1 (SC:CC)]	Inhibition of the proliferation	(36)
Human umbilical cord	Ovarian cancer cells line	In vitro co-culture [1:1 (SC:CC)] 24-96 hours	Inhibition of the proliferation	(46)
Human umbilical cord	Hepatocellular carcinoma cell line	In vitro co-culture [1:1 (SC:CC)] and CM (1:1 and 1:20); in vivo (xenograft model; 1:1 SC-CC injection)	Inhibition of the proliferation	(49)

Table 1. Study summaries showing the effects of MSCs on cancer proliferation (continue)

Human umbilical Cord	Esophageal cancer cell line	In vitro co-culture [0:1, 1:1, 2:1, 5:1 (SC:CC]	Inhibition of the proliferation	(50) (Abstract)
Human umbilical Cord	Esophageal cancer cell line	In vitro co-culture [1:1 (SC:CC)] and CM (1:1); in vivo (xenograft model; 5 × 10^6 cells per injection)	Promotion of the proliferation	(47)
Human umbilical Cord blood	Human chronic myeloid leukemia cell line (K562)	Co-culture of 5.000 K562 cells /well with human UC-MSCs at 1:1, 1:5, 1:10 and 1:100	Inhibition of the proliferation in a dose-dependent	(33)
Human umbilical Cord	Human breast cancer cell lines	Conditioned medium (0, 10 or 20% CM)	Promotion the proliferation and migration (via activation of the ERK pathway.)	(26)
Human bone marrow	Kaposi's sarcoma	In vitro [1:6 (hUCMSC: MDA231)] and in vivo (xenograft model; 0.5×106 cells per injection)	Inhibition of the proliferation	(51)
Human bone marrow	Head and neck cancer cell lines (SCC-25)	Co-culture of SCC-25 cells with human BM-MSCs at 1:1 ratio	Promotion of the proliferation	(27)
Human bone marrow	Primary patient-derived human acute myeloid leukemia cells	Culture of MSCs (2 x 104 cells/well) 1 x 106 with AML cells in Transwell system for 3 days	Promotion of the proliferation	(24)
Human bone marrow	Human brain tumor cell lines	Co-culture with Transwell system and conditioned media usage	Decrease in tumor proliferation	(40)
Human bone marrow	Colon cancer cell lines (HCT116 and LOVO CRC)	Condition media obtained from 1 x 106 MSCs	Increase in proliferation	(28)
Rat bone marrow	Human chronic myeloid leukemia cell line (K562)	Co-culture of K562 and MSCs at 10:1 ratio for 7 days	Inhibition of cell proliferation	(32)
Human adipose and bone marrow	Pancreas, liver, colon, prostate cell lines	Co-culture of MSC-CC at different ratio (1:1, 1:5, 1:100) and conditioned media; *in vitro* and *in vivo* model	Inhibition of the proliferation in a dose-dependent	(30)
Human palatine tonsil tissue	Head and neck squamous cell carcinoma cell lines (PNUH-12 and SNU-899)	48 hours culture of MSC-CC at different ratio (1:20, 1:10, 1:5, 1:2)	Inhibition of the proliferation in a dose-dependent	(38)
Amniotic membrane	Lung carcinoma cells (A549)	Conditioned media and heat-treated conditioned media (at 43°C for 45 minutes and then at 37°C for 24 hours)	The conditioned medium led to significant proliferation of tumor spheroids. Heat treated conditioned medium resulted in a reduction in both spheroid diameter and cell proliferation	(31)
Amniotic fluid and adipose tissue	Human kidney (786-0) and bladder (T24) carcinoma cell lines	24, 48, 72 hours incubation with conditioned media	It reduces the viability of bladder and kidney cancer cells, has been demonstrated to induce cell cycle disruptions in T24 cells; however, it may play a role in developing resistance to anticancer agents.	(39)

SC: stem cell; CC: cancer cell

The anti-tumor function of MSCs on hematological cancers has been less studied than on solid cancers and less data are available. However, there are data showing that MSCs inhibit (32, 52-54), induce proliferation on hematological cancers (52).

Results obtained by administering mouse bone marrow-derived MSCs to hematological cancer cells indicate that it may be safe and efficient in treating hematological malignancies (54). Additionally, proliferative effects of adipose tissue-derived MSCs on hematological cancer cell lines by secreting DKK-1 (dickkopf-1), a negative regulator of the WNT signaling pathway, which is known to be effective in tumor formation, are presented (55). Data have been provided that human bone marrow mesenchymal stem cell application has an anti-tumoral effect in the xenograft model of non-Hodgkin lymphoma (56), whereas it supports tumor growth of adipose tissue-derived MSCs in animal models of acute lymphoblastic leukemia cells (57). In a recent study, it was determined that bone marrow-derived MSCs caused a strong increase in the number of cells in the G0/G1 phase of stem cells after long-term co-culture with the K562 hematological cancer cell line, and significantly late apoptosis was induced in K562 cells. Analysis of 34 different cytokines suggested that the increase in metalloproteinase-1 tissue inhibitor (TIMP-1) and cytokine-stimulated neutrophil chemoattractant-1 (CINC-1) may be effective in the inhibition of K562 cell proliferation via BAX and caspase-3 cascade signaling pathway (32). It is known that secreted growth factors and cytokines vary according to the type of cell and culture conditions; however, the kind of cytokine, which is significant in cancer cell death, depends on both the stem cell and the target cancer cell type. It is known that the density of MSCs significantly affects morphology, proliferation rate and secreted factors. It has been suggested that the antitumor actions observed in solid cancers are associated with a low MSC dose. A similar association has not yet been proposed for hematological malignancies, possibly due to the paucity of studies (58).

In line with the data from different studies, the cytokines responsible for cancer cell death vary according to the stem cell and target cancer cells. Although a reduction in the growth curve of cancer cells due to UCMSC was observed, BMMSCs have been shown to stimulate the growth and metastatic ability of melanoma cells in a genetic tumor model. It has also been shown that MSCs participate in tumor stroma formation, thereby promoting tumor growth. The reasons underlying these conflicting results include the fact that MSC cultures contain differentiated cell populations, different pathophysiological conditions originating from the MSC obtained donors, or potential feeder cell contamination that may be present in the MSC culture supports different cellular processes in cancer cells (29).

MSCs show their therapeutic functions with immunosuppressive, anti-apoptotic, anti-fibrotic, angiogenic and anti-inflammatory effects through paracrine factors such as secreted growth factors, cytokines and extracellular vesicles. Tumors apply chemoattractive effects on MSCs, facilitating their movement to the tumor niche. One of the most frequently researched signaling pathways in the mobilization of MSCs into the tumor microenvironment has been identified as C-X-C Motif Chemokine Ligand 12/C-X-C chemokine receptor type 4 (XCL12/CXCR4). However, migration of MSCs towards cancerous tissue is also controlled by many molecules, including cytokines such as IL8, growth factors such as TGFβ1 or platelet-derived growth factor (PDGF), and extracellular matrix molecules such as MMP-2. Upon reaching the tumor site, MSCs interact with cancer cells through direct and indirect mechanisms that influence tumor development and growth. The paracrine effects of MSCs are one of the major mechanisms involved in cancer regulation and are regulated by many factors, such as growth factors and cytokines. It ultimately affects cellular processes including proliferation, survival, angiogenesis and immunosuppression/immunomodulation of cancer cells. Paracrine agents can be secreted directly into the extracellular space or are packaged into extracellular vesicles for release into the tumor environment. At the same time, MSCs can induce cell cycle arrest by inhibiting various cellular mechanisms such as the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway and negatively affect cancer proliferation (8).

3. Mesenchymal Stem Cells Conditioned Media

Co-culture studies can sometimes be contradictory due to the likely growth superiorities of one cell kind over another, caused by the culture medium, rather than a true anti-cancer effect. As a result of recent studies, it is known that MSCs generally exert their therapeutic effects with various paracrine factors such as cytokines, growth factors, extracellular matrix proteins and different extracellular vesicles secreted by these cells. MSC conditioned medium (MSC-CM), also called MSC secretome, constitutes an intensive source of paracrine factors. So far, it has been extensively studied for regenerative treatments in various diseases such as cardiovascular diseases, wound healing and bone regeneration (59, 60).

Using stem cells in translational oncology and regenerative medicine has many advantages. Besides, it has some disadvantages that come with the use of cells, such as immunological responses in the recipient after administration, movement of the cell to non-target tissue and a decrease in its regenerative potential. In vitro culture of target stem cells is mandatory to obtain the required amount of cells for clinical applications. However, factors such as minimal media variability in culture conditions and changing pH conditions encountered by enlarged stem cells following the transplantation process adversely affect their regenerative capacity. It has also been reported that in vitro cultured stem cells acquire properties similar to cancer cells when applied to normal tissues (61).

The important advantage of using CM as a cell-free cellular therapy is no requirement of donor-recipient compatibility, which is important in cellular therapy. At the same time, MSC-CMs will have an advantage that is more accessible and applicable as it will require less controlled conditions as an

application procedure when compared to the use of stem cells, which require sterile and special production conditions in the application process to the patient. In addition, it will be easily packaged, commercialized after being freeze-dried or lyophilized, and will be more accessible and portable as it will eliminate the need for cryopreservation compared to cell-based therapy (59). Based on all these properties, CMs are promising candidates as biological pharmaceuticals, but with many unknowns (62).

Since stem cells obtained from different sources have the potential to secrete different paracrine factors, the choice of tissue in which stem cells will be used in the treatment of diseases is important (59). In addition, different paracrine factors can be secreted at different rates according to the age of the cells and the culture status (hypoxic / normoxic, time taken for MSC-CM collection, 2D/3D cultures) (61) . Severe stress levels to which cells may be exposed can induce the secretion of resistance-related factors to toxic conditions. It has also been reported that the secretome obtained in serum-free conditions will accelerate the secretion of angiogenic factors. In a study, it was shown that 3D culture of cells and hypoxic culture conditions changed secretion levels in conditioned media. In particular, CMs from 3D spheroid cultures showed significant differences compared to 2D cultures in terms of 11 cytokines and IL-2Rα (59, 62, 63).

Different studies have been conducted to determine the effects of conditioned media of MSCs on cancer cell growth and different results have been observed (35, 64). It has been shown that CMs obtained from human lung-derived mesenchymal stem cells inhibit tumor cell growth (65), CMs obtained from human Wharton's jelly-derived MSC (hWJMSCs) had no effect on proliferation and apoptotic potential of A549 lung cancer cells (66), and CMs obtained from BMMSC can inhibit lung cancer cell proliferation and induce apoptosis of tumor cells in vitro (67).

In another research evaluating the anti-cancer effect of the secretome of hUCMSCs on breast cancer cells, it was shown to cause depending on the dose administered cytotoxic effect on the cancer cell line (68). Besides, the findings of in vitro studies investigating the therapeutic potential of MSCs from different tissues on ovarian cancer cell lines showed variability in the effects of MSC secretomes from different tissues, and conditioned media obtained from hUCMSCs was more effective in necrosis, while the supernatant derived from hATMSC was found to play a more important role in apoptosis. As a result, it has been reported that MSC-CMs cause a significant decrease in tumor markers (CA-125, LDH, beta-HCG) (36).

4. Mesenchymal Stem Cells Exosomes

Exosomes, which are secreted by cells and are approximately 30-100 nm in diameter, are defined as lipid bilayer extracellular membrane vesicles found in numerous body fluids, including blood, amniotic fluid, cerebrospinal fluid, saliva, and lymph and secreted by a variety of cells in culture, including epithelial cells, stem cells, immune cells, and tumor cells (69, 70). These exosomes are known to function in the regulation of cellular interaction through various molecules, including cytokines, growth factors, nucleic acids such as protein, lipid, mRNA, miRNA, lncRNA (71) . At the same time, most of the exosomes have tetraspanins such as CD81, CD63 and CD9, heat shock proteins such as HSP60, HSP70 and HSP90, ALG2-interacting protein X (ALIX), tumor susceptibility gene 101 (TSG101), and additionally tissue-specific proteins from which they are derived (72).

The molecular composition of exosomes varies considerably according to the donor cell, epigenetic changes, and physiological and pathological conditions to which the cell is exposed. Exosomes derived from MSCs also have anti-inflammatory, immunomodulatory and regenerative properties, which are similar to MSCs (71) and have been reported to have both pro-tumorigenic and anti-tumoral effects (73).

There are studies reporting that MSCs and MSC-CMs induce or inhibit tumor cell proliferation, migration and growth and are discussed in detail in the sections above. Studies investigating the effect of MSC-derived exosomes on tumor proliferation and migration have accelerated in recent years, and it has not been resolved whether or not they contribute. In a study in which MCF7 breast cancer cells were treated with MSC exosomes, it was determined that MSC exosomes applied at different concentrations induced an increase in cell migration in a dose-dependent manner (74). However, MSC exosomes derived from mouse bone marrow have been shown to inhibit angiogenesis as a result of downregulation of vascular endothelial growth factor (VEGF) expression in mouse breast cancer cell lines in in vitro and in vivo experimental models (75).

The results of the study evaluating the effect of exosomes obtained from hBMSCs on human gastric and colon cancer cell lines showed that the expression levels of VEGF and CXCR4, which are known to be important in tumor angiogenesis, growth and metastasis, was increased by the activation of ERK1/2 and p38 MAPK pathways. Besides, they showed the induction of tumor growth and promoting angiogenesis in *in vivo* models (76). Similarly, it has been shown to induce proliferation in gastric cancer cells and increase the migration and metastatic potential of cancer cells by stimulating epithelial-mesenchymal transition (77).

In addition to studies supporting that MSC-derived exosomes stimulate tumor growth, there are also a significant number of studies that inhibit tumor growth. In vitro and in vivo experimental models in bladder cancer cells demonstrated that the increase in caspase-3 expression and decrease in Akt phosphorylation of microvesicles derived from hWJMSCs induce apoptosis and cause cell cycle arrest in cancer cells (78). Another data demonstrating the antitumoral effect of exosomes

was obtained from lung cancer xenograft models, and it was demonstrated that MSC-EVs increase apoptosis in lung cancer cells and have the potential to be a therapeutic agent (79).

Despite inconsistent results regarding the effect of exosomes on cancer proliferation, the use of these molecules as carriers for the specific and safe delivery of drugs or nucleic acids (miRNAs, siRNAs, and LncRNAs) is increasing interest in exosomes. Particularly, their nanoscale dimensions and their use in the intercellular transfer of various cellular components provide important advantages in the efficient transfer of therapeutic agents to cancer cells. It has been reported that siRNA-loaded exosomes targeting oncogenic Kras have a strong anti-tumoral effect in models of pancreatic ductal adenocarcinoma (PDAC), and importantly, it has been shown that large-scale production under good manufacturing practice (GMP) conditions in cancer treatment may be possible (80).

5. Clinical Applications of MSCs in Cancer Therapy

A limited number of clinical studies have been conducted, inspired by successful preclinical results in the cancer treatment of MSCs. In the study conducted by MD Anderson Cancer Center as a Phase 1 clinical trial, it was aimed to find the highest tolerable dose of human mesenchymal stem cells containing interferon beta (MSC-INFβ) that can be given to patients with ovarian cancer and to test the safety of MSC-INFβ (NCT02530047). Another Phase 1 clinical study was conducted to determine the maximum tolerated dose of allogeneic bone marrow-derived MSCs loaded with oncolytic adenovirus DNX-2401 in the treatment of glioma patients (NCT03896568). In addition to its potential for direct use in cancer treatment, there are clinical studies covering MSC applications to eliminate various side effects such as acute renal failure and cardiomyopathy that develop after treatment protocols such as chemotherapy and radiotherapy used in cancer treatment (NCT02509156, NCT03874572, NCT01275612, NCT02814864). The clinical studies carried out both for the treatment of MSCs and for the elimination of their side effects are summarized in Table 2. Despite the clinical trials, the lack of published studies reveals the need for more progress and more data to be obtained before MSCs can be used in cancer treatment.

Table 2. MSC clinical trials in the treatment of cancer and treatment-related adverse events

NTC Number	Treatment	Cancer type	Clinical stage
NCT01045382	Mesenchymal stem cells and HLA-mismatched allogeneic hematopoietic cells	Hematological malignancy	Phase II
NCT01092026	Cord blood transplantation with mesenchymal stem cell coinfusion	Hematological malignancy	Phase I/II
NCT01129739	Safety and efficacy study of umbilical cord/placenta-derived mesenchymal stem cells	Myelodysplastic syndromes	Phase II
NCT01844661	Safety and efficacy of bone marrow-derived autologous mesenchymal stem cells infected with ICOVIR5, an oncolytic adenovirus (CELYVIR)	Solid Tumors Metastases	Phase I/II
NCT01983709	Allogeneic human bone marrow derived mesenchymal stem cells	Prostate cancer	Phase I
NCT02270307	Mesenchymal stromal cells and cyclophosphamide as a GVHD prophylaxis	Leukemia Multiple Myeloma	Phase II/III
NCT02079324	Genetically modified mesenchymal stem cell (GX-051)	Head and Neck Cancer	Phase I
NCT02068794	Genetically modified mesenchymal stem cell (Oncolytic Measles Virus Encoding Thyroidal Sodium Iodide Symporter; MV-NIS)	Recurrent Ovarian Primary Peritoneal or Fallopian Tube Cancer	Phase I/II
NCT02181478	Cord blood and mesenchymal stromal cells	Hematological malignancy	Early Phase I
NCT02530047	Mesenchymal stem cells containing interferon beta (MSC-INFβ)	Ovarian cancer	Phase I
NCT03184935	Umbilical cord mesenchymal stem cells	Myelodysplastic syndromes	Phase I/II
NCT03298763	Mesenchymal stem cells expressing TRAIL	Adenocarcinoma of Lung	Phase I/II
NCT03608631	Mesenchymal stromal cells-derived exosomes with KrasG12D siRNA	Pancreatic cancer	Phase I
NCT03896568	Allogeneic bone marrow human mesenchymal stem cells loaded with a tumor selective oncolytic adenovirus, DNX-2401,	Glioma	Phase I
NCT02509156	Safety and efficacy of allogeneic mesenchymal stem cells	Anthracyclines-induced Cardiomyopathy	Phase I
NCT03874572	Evaluating the safety and feasibility of allogeneic mesenchymal stem cells	Radiation-induced hyposalivation and xerostomia	Phase I
NCT01275612	Ex-Vivo expanded mesenchymal stem cells	Chemotherapy-Induced Acute Kidney Injury	Phase I
NCT02814864	Mesenchymal stromal cell	Radiation-induced Hemorrhagic Cystitis	Phase II

6. Conclusion

This review focuses on the potential roles of mesenchymal stem cells, paracrine factors released from MSCs, and exosomes in cancer therapy, whose use in the treatment of many diseases in regenerative medicine is supported by clinical and preclinical studies. In the light of the data obtained so far, the potential effect of MSCs, paracrine factors released from MSCs and exosomes on cancer cells remains unclear due to the influence of various factors on tumor development and the variability between experimental applications. The fact that the results of the limited number of clinical studies have not been published appears to be an important shortcoming. Inconsistent results for the potential use of MSCs for cancer treatment reveals that their potential to be used in cancer treatment should be supported by more experimental processes and clinical studies.

Conflict of interest

The authors declared no conflict of interest.

Funding

No funding was used for the study.

Acknowledgments

The author would like to thank Esra Albayrak for editing the writing.

Authors' contributions

Concept: M.Y., Design: M.Y., Data Collection or Processing: M.Y., Analysis or Interpretation: M.Y., Literature Search: M.Y., Writing: M.Y.

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