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REVIEW

Clinical application of stem cells: An update 2015

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Abstract— Stem cell transplantation has the long history of more than 50 years from the first bone marrow transplantation in 1957. From the 2000s, clinical applications of stem cells significantly increased with more diseases and more patients treated with stem cells. Both autologous stem cells and allogeneic stem cells as well as adult stem cells and induced pluripotent stem cells (iPSCs), and both in vitro non-expanded stem cells and in vitro expanded stem cells were clinically applied. For adult stem cells, besides hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), neural stem cells, endothelial progenitor cells, limbal stem cells… also were used in the treatment of some diseases. To the year 2015, applications of MSCs have dramatically increased when some MSCs-based drugs that were approved and commercialized in some countries. About iPSCs, Japanese scientists also firstly applied the iPSCs in treatment of ophthalmological diseases. Currently, the European Medicines Agency approved the first expanded stem cell therapy to repair damaged cornea in the Europe. This review aimed to summarize, update clinical applications of stem cells to 2015.

Keywords— Stem cells, clinical application, adult stem cells, induced pluripotent stem cells, stem cell transplantation

INTRODUCTION

As one of the four bases of healthcare science, stem cell therapy offers advanced treatment for degenerative diseases as well as for some genetic disorders. Initially, bone marrow was used as a source of hematopoietic stem cells. To date, stem cell types which have been used in clinical trials include HSCs, mesenchymal stem cells, neural stem cells, epidermal stem cells, endothelial progenitor cells, limbal stem cells, embryonic stem cells, and induced pluripotent stem cells. Their use in clinical trials strongly increased approximately 10 years ago. As per clinicaltrials.gov, more than 5000 clinical trials use stem cells for treatment of more than 50 different diseases (**Fig. 1, Table 1**). More importantly, from 2010 onwards, approximately 12 stem-cell based products have been approved for treatments, some of them are regarded as stem cell drugs **(Table 2).**

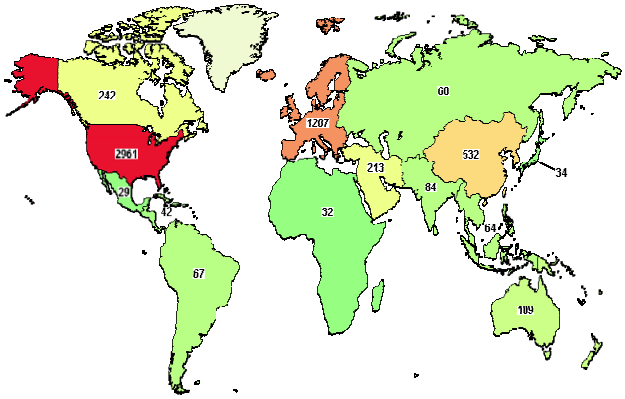

Figure 1. Stem cell therapy clinical trials in the world (according to clinicaltrials.gov, Jan 2016). More than 5000 clinical trials were performed at some countries as Table 1.

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Table 1. Stem cell clinical trials were distributed over the world

Region Name	Numbers of clinical trials
World	**5348**
Africa	32
Central America	42
East Asia	532
+ Japan	34
Europe	1207
Middle East	213
North America	3079
+ Canada	242
+ Mexico	29
+ United States	2961
North Asia	60
Pacifica	109
South America	67
South Asia	84
Southeast Asia	64

Table 2. Some stem cells based products approved for treatment

Names of products	Kinds of stem cells	Indication	Type of transplantation	Company of production	Country of approval
Cartistem	HSCs from UCB	Osteoarthritis	Allo	Medipost	Korea
MPC	MSCs	N/A	Allo	Mesoblast	Australia
Cupistem	MSCs from AT	Crohn's disease	Auto	Anterogen	Korea
Prochymal	MSCs from BM	GVHD	Allo	Osiris Therapeutics	Canada
AlloStem	MSCs from BM	Bone and cartilage degeneration	Allo	AlloSource	US
HeartiCellGram-AMI	MSCs from BM	Post heart infarction	Auto	FCB PharmiCell	Korea
Osteocel Plus	MSCs from BM	Bone and cartilage degeneration	Allo	NuVasive	US
Trinity Evolution	MSCs from BM	Bone and cartilage degeneration	Allo	Orthofix	US
CardioRel	MSCs from BM	Post heart infarction	Auto	Reliance Life Science	India
HoloClar	Limbal stem cells	Injured cornea	Auto	HoloStem	EU
HemaCord	HSCs	N/A	Allo	NewYork Blood Center	US
DuCord	HSCs	N/A	Allo	Duke University and Carolinas Blood Bank	US
N/A: Non indication					

Clinical application of HSCs

HSC transplantation is now considered to be standard treatment for some types of abnormal hematological conditions, including multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, β-thalassemia, and sickle cell anemia (Giralt et al., 2014). HSCs from bone marrow, peripheral blood, and cord blood are used to clinically treat these hematological diseases (Cheuk, 2013). In contrast to HSCs that found in bone marrow(BM) and in umbilical cord blood (UCB), HSCs from peripheral blood were collected after stimulation with cytokines such as granulocyte colony-stimulating factor(G-CSF) to mobilize the HSCs from BM to peripheral blood. In recent studies, HSCs from BM could be mobilized by chemicals used in chemotherapy, called chemomobilization, or by using plerixafor (AMD3100) (Giralt et al., 2014) or BIO5192- a small-molecule inhibitor of integrin α_4 which interrupts the VCAM-1–VLA-4 (integrin α_4) axis (Ramirez et al., 2009) (**Fig. 2**). Current clinical trials have also used HSCs for solid tumor treatments and for curing HIV. Although initial results have shown promise, more clinical trials need to be performed to confirm these results before routine therapeutic use.

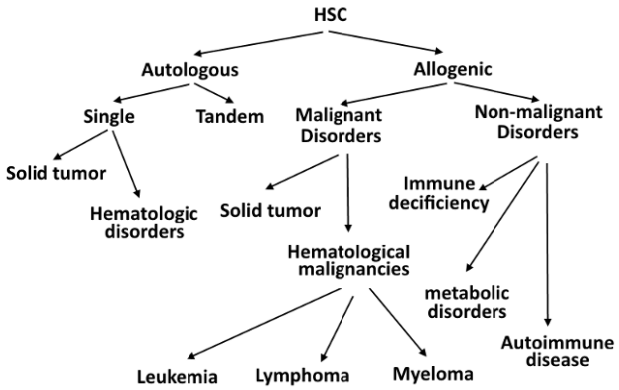

Figure 2. Indications for HSCT.

MSC-based therapies

For the past five years, MSC-based therapies have been widely used in clinical applications as one of two main approaches: (1) approved MSC-based products and (2) clinical trials. Some MSC-based products have been approved for clinical applications in several countries for treating diseases involving both autologous and allogeneic transplantation. They have significantly contributed to the growth of MSCs-based therapies and include the following: CARTISTEM® (a combination of human umbilical cord-MSCs (UC-MSCs) and sodium hyaluronate for cartilage regeneration), CardioRel® (autologous product designed for early or planned intervention in patients of myocardial infarction), Trinity® Evolution™ (allograft of cancellous bone containing viable adult stem cells and osteoprogenitor cells within the matrix), Osteocel® Plus (allograft cellular bone matrix that retains its native bone-forming cells, including MSCs and osteoprogenitors for the repair, replacement, and reconstruction of skeletal defects), Hearticellgram®-AMI (bone marrow-derived MSCs (BM-MSCs) used to treat acute myocardial infarction (MI) through intracoronary injection), AlloStem (demineralized allograft bone combined with adipose-derived MSCs for general bone grafting applications), and Prochymal (first stem cell drug approved for use in Canada for acute graft-versus-host disease(GVHD) (**Fig. 3**).

In addition to approved MSCs-based products, MSCs itself have been used in disease treatment through clinical trials. According to clinicaltrials.gov, approximately 542 registered clinical trials have used MSCs for treatment (**Fig. 4, Table 3**). The first clinical trial using *in vitro* expanded MSCs was performed in 1995, in which 15 patients were treated with autologous stem cells (Lazarus et al., 1995). According to clinicaltrials.gov, almost all current trials are in Phase I, Phase II, or Phase I/II, and some of these trials are in Phase II or Phase II/III. Diseases treated by MSCs-based therapies include hematological diseases, GVHD, diabetes, liver diseases, kidney diseases, lung diseases, cardiovascular diseases, bone and cartilage diseases, neurological diseases, Crohn's disease, and lupus erythematosus.

Figure 3. Some approved MSC-based products in some countries. (A) Cartistem; (B) Trinity Evoluation; (C) Osteocel; (D) Prochymal.

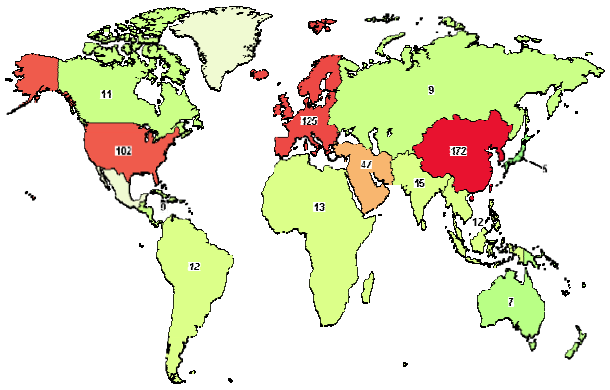

Figure 4. Clinical trials using mesenchymal stem cells.

Table 3. MSC-based clinical trials in a completed status

Pathology	Clinical status completed						
Overall	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Phase IV	N D
Hematological disease	1	2	1	0	0	0	0
GVHD	0	4	2	0	1	0	0
Diabetes	1	1	0	0	0	0	1
Liver disease	0	3	0	0	0	0	0
Kidney disease	0	0	0	0	0	0	1
Lung disease	3	0	1	0	0	0	0
Cardiovascular disease	2	11	4	1	0	0	1
Bone and cartilage disease	12	8	3	1	2	0	3
Neurological disease	9	8	2	0	0	0	1
Chron's disease	0	1	1	1	0	0	1
Lupus ErythemaErythematosus	0	0	0	0	0	0	0
Other	3	2	1	0	11	1	2
Overall	**31**	**40**	**15**	**3**	**4**	**1**	**10**

Limbal stem cells

Limbal stem cells (LSCs) have had a long history of clinical applications. LSCs and autograft of limbal tissues were employed by Kenyon and Tseng since 1989 (Kenyon and Tseng, 1989). Both fresh limbal tissues (Rao et al., 1999; Shimazaki et al., 2006; Tseng et al., 1998) and cultivated limbal tissues (Rama et al., 2001; Sangwan et al., 2005a; Sangwan et al., 2005b; Tseng et al., 2002) were clinically used. A common procedure was to use limbal tissue collected from healthy eyes and transplant it into injured eyes. However, this procedure was associated with injuries in healthy eyes-donors after the collection of limbal tissue. Recently, allotransplantation, that uses limbal tissue from donors, has been developed. Ang et al. (2007) showed that a limbal allotransplant helped decrease stromal scarring and improved vision in the transplanted eyes. Cultivated limbal epithelial transplantation also significantly improved injury treatment with great success (**Table 4**). In 2015, the European Commission approvedHoloclar®, the first advanced therapy medicinal product (ATMP) containing LSCs, for clinical use in Europe.

Table 4. Summary of reports on clinical outcome of CLET

No.	Group	Year	Number of eyes	Fllow-up months	Success (%)
1	Schwab et al	2000	14	13	71.4
2	Rama et al.	2001	18	12-17	77
3	Shimazki et al.	2002	13	10	46.2
4	Daya et al.	2005	10	28	70
5	Sangwan et al.	2005	15	8.3	93
6	Sangwan et al	2006	88	18.3	73.1

Neural stem cells

Neural stem cells (NSCs) are adult stem cells that can differentiate into glial cells and neurons. Neurological and central nervous system (CNS) disorders include groups of numerous diseases. According to clinicaltrials.gov, approximately 1000 clinical trials tested NSCs for treatments (**Table 5**). Recently, Phase I and Phase II clinical trials were conducted using NSCs for treatment of CNS disorders. Most of these studies used allogenic NSCs from human fetal tissues. The first clinical trials of NSCs, held in May 2006 at Oregon Health and Science University (OHSU, Portland, OR, USA), involved fetal tissue-derived NSCs for lysosomal storage diseases.

NSCs were also used to treat CNS diseases such as Pelizaeus-Merzbacher disease (PMD), intramedullary spinal cord transplantation of human HuCNS-SC neurospheres in subjects with thoracic (T2-T11) spinal

cord trauma, chronic spinal cord injury, Lou Gehrig's disease, ALS, disabled ischemic stroke, Parkinson's diseases, Alzheimer's diseases, and spinal cord injury. To date, there has been a single clinical trial using human ESC-derived neural cells for CNS injury treatment. In 2010, Geron Corporation started Phase I clinical trials using human ESC-derived oligodendrocyte progenitors (GRNOPC1 cells) in patients with neurologically complete, subacute spinal cord injury (*ClinicalTrials.gov identifier:NCT01217008*) (Lebkowski, 2011; Okamura et al., 2007). In 2013, AsteriasBiotherapeutics, Inc., a subsidiary of BioTime, purchased the Geron Corporation's stem cell division and announced the resumption of its spinal cord trial.

Table 5. Clinical trials involving NSCs for neurodegenerative diseases

NCT number	Title	Recruitment	Conditions	Interventions	Sponsor/Collaborators	Phases	Enrollment	Start date	Completion date
NCT00337636	Study of HuCNS-SC Cells in Patients With Infantile or Late Infantile Neuronal CeroidLipofuscinosis (NCL)	Completed	Neuronal CeroidLipofuscinosis	Biological: HuCNS-SC	StemCells, Inc.	Phase 1	6	May 2006	September 2009
NCT01005004	Study of Human Central Nervous System (CNS) Stem Cells Transplantation in Pelizaeus-Merzbacher Disease (PMD) Subjects	Completed	Pelizaeus-Merzbacher Disease	Biological: HuCNS-SC cells implantation	StemCells, Inc.	Phase 1	4	November 2009	December 2012
NCT01151124	Pilot Investigation of Stem Cells in Stroke	Active, not recruiting	Stroke	Biological: CTX0E03 neural stem cells implantation	ReNeuron Limited	Phase 1	12	June 2010	March 2015
NCT01217008	Safety Study of GRNOPC1 in Spinal Cord Injury	Completed	Spinal Cord Injury	Biological: hES-derived GRNOPC1 implantation	AsteriasBiotherapeutics, Inc.	Phase 1	5	October 2010	July 2013
NCT01238315	Safety and Efficacy Study of HuCNS-SC in Subjects With Neuronal CeroidLipofuscinosis	Withdrawn	Neuronal CeroidLipofuscinosis	Biological: HuCNS-SC cells implantation	StemCells, Inc.	Phase 1	0	November 2010	April 2011
NCT01321333	Study of Human Central Nervous System Stem Cells (HuCNS-SC) in Patients With Thoracic Spinal Cord Injury	Active, not recruiting	Thoracic Spinal Cord Injury|Spinal Cord Injury|Spinal Cord Injury Thoracic|Spinal Cord Trauma	Biological: HuCNS-SC cells implantation	StemCells, Inc.	Phase 1-2	12	March 2011	December 2015
NCT01348451	Human Spinal Cord Derived Neural Stem Cell Transplantation for the Treatment of Amyotrophic Lateral Sclerosis	Active, not recruiting	Amyotrophic Lateral Sclerosis	Biological: human neural spinal cord stem cells implantation	Neuralstem Inc.	Phase 1	18	January 2009	August 2014
NCT01640067	Human Neural Stem Cell Transplantation in Amyotrophic Lateral Sclerosis (ALS)	Recruiting	Amyotrophic Lateral Sclerosis	Biological: Human Neural Stem Cells implantation	AziendaOspedaliera Santa Maria, Terni, Italy|AziendaOspedalieroUniversitaria Maggiore dellaCarita|Università di Padova Italy	Phase 1	18	December 2011	September 2016

NCT number	Title	Recruitment	Conditions	Interventions	Sponsor/Collaborators	Phases	Enrollment	Start date	Completion date
NCT01725880	Long-Term Follow-Up of Transplanted Human Central Nervous System Stem Cells (HuCNS-SC) in Spinal Cord Trauma Subjects	Enrolling by invitation	Spinal Cord Injury	Observation	StemCells, Inc.	Phase 1-2	12	November 2012	March 2019
NCT01730716	Dose Escalation and Safety Study of Human Spinal Cord Derived Neural Stem Cell Transplantation for the Treatment of Amyotrophic Lateral Sclerosis	Enrolling by invitation	Amyotrophic Lateral Sclerosis	Biological: Human spinal cord stem cell implantation	Neuralstem Inc.	Phase 2	18	May 2013	April 2014
NCT01772810	Safety Study of Human Spinal Cord-derived Neural Stem Cell Transplantation for the Treatment of Chronic SCI	Not yet recruiting	Spinal Cord Injury (SCI)	Biological: Human spinal cord stem cells implantation	Neuralstem Inc.	Phase 1	8	May 2014	March 2016
NCT02117635	Pilot Investigation of Stem Cells in Stroke Phase II Efficacy	Not yet recruiting	Ischaemic-Stroke|CerebralInfarction|Hemiparesis|Arm Paralysis	Biological: CTX DP	ReNeuron Limited	Phase 2			

Endothelial progenitor cells

Endothelial progenitor cells (EPCs) were first discovered in 1997. Although their classification as stem cells is controversial, they are considered to be an important source of cells used in regenerative medicine. These cells can differentiate into specific cell types but are limited in self-renewal. EPC-based therapies have been tested in angiogenesis therapy for critical ischemic tissues, post injury vascular endothelial regeneration, and in *in vivo* tissue engineering. There are two types of EPCs, namely, early EPCs and late EPCs. The early EPCs are spindle-shaped cells that attain peak growth at approximately 2 weeks and die by 4 weeks. Late EPCs appear only as a cobblestone monolayer with near-complete confluence, exhibit exponential population growth without senescence over 4-8 weeks and live for up to 12 weeks. EPCs have been clinically tested for treating diseases (Jujo et al., 2008; Lee and Poh, 2014; Losordo et al., 2007). To date, all clinical trials using EPCs involve autologous transplantation (**Table 6**). Allogeneic transplantation has been tested in animal models and can be applicable to humans in the near future.

Table 6. Summary of clinical trials: Effect of heart failure on endothelial progenitor cells

Ref.	Subjects	EPCs (number/function)	Findings
Valgimigli et al (Valgimigli et al., 2004)	45 healthy controls 91 CHF	$CD34^+$, $CD34^+$/$CD133^+$/KDR^+ (flow cytometry)	$CD34^+$ and $CD34^+$/$CD133^+$/KDR^+ are significantly elevated in CHF patients compared to controls EPC number is negatively correlated with NYHA functional class
Nonaka-Sarukawa et al (Nonaka-Sarukawa et al., 2007)	22 healthy controls 16 mild CHF 10 severe CHF	$CD34^+$ (flow cytometry)	$CD34^+$ is significantly higher in mild CHF compared to severe CHF
Michowitz et al (Michowitz et al., 2007)	107 CHF	CFU	CFU is the independent predictor for CHF CFU is also negatively correlated with NYHA functional class

EPC: Endothelial progenitor cells; CHF: Congestive heart failure; CFU: Colony forming unit; NYHA: New York Heart Association.

Embryonic stem cells and induced pluripotent stem cells

Human embryonic stem cells (ESCs) as well as induced pluripotent stem cells (iPSCs)-based therapies have also moved to clinical trials despite ethical issues. ESCs and IPSCs have been used in two forms, including ESCs and ESCs-derived cells. Human ESCs-derived retinal pigment epithelium was used to treat age-related macular degeneration and Stargardt's macular dystrophy (Schwartz et al., 2015) in Phase I/II (**Table 7**). Preliminary results after 1 year of treatment showed that visual acuity improved (9-19 letters in three patients) and remained stable (+1 letter in one patient) (Song et al., 2015). Besides, ESCs and iPSCs were also used to treat other diseases such as spinal cord injury, geographic atrophy secondary to myopic macular degeneration, Stargardt macular degeneration of retina, dry macular degeneration of retina, wet macular degeneration of retina, diabetes Type I, heart failure, and immunotherapy vaccine for lung cancer. Compared to adult stem cells, ESCs have undergone fewer clinical trials in a limited number of patients but it is expected that they will be widely employed in the near future.

Table 7. Clinical trials involving ESCs/iPSCs

Indication	Cell source	Institution	Country	Start date	Finish date	Subjects
Spinal cord injury	hESC	Geron	USA	October 2010	July 2013	5
		Asterias	USA	March 2015	June 2018	13
Immunotherapy vaccine for lung cancer	hESC	Asterias	UK	Not defined	Not defined	Not defined
Geographic atrophy secondary to myopic macular degeneration	hESC	Ocata	USA	April 2014	April 2015	Not defined
Stargardt macular degeneration of retina	hESC	Ocata	USA	July 2012	December 2030	13
			UK	Nov 2011	Dec 2015	16
Dry macular degeneration of retina	hESC	Ocata	USA	July 2012	Dec 2030	13
		Cell Cure Neurosciences	Israel	April 2015	Aug 2017	15
	iPSC	Riken CBD	Japan	Oct 2013	Not defined	6
Wet macular degeneration of retina	hESC	The London Project to Cure Blindness	UK	Aug 2015	Oct 2016	10
Diabetes type I	hESC	ViaCyte	USA	Sept 2014	Aug 2017	40
Heart failure	hESC	APHP	France	June 2013	June 2017	6

CONCLUSION

Stem cell therapy has strongly developed since the 2010s to date. Besides hematopoietic stem cell transplantation, mesenchymal stem cell (MSC) transplantation becomes a new choice for regenerative medicine. These initial results from clinical trials of MSC transplantation showed that MSC transplantation is opening a new revolution of stem cell therapy in next decades. Embryonic stem cells as well as pluripotent stem cells have vastpotential for treatment, but they only could become treatment options when the problems about in vivo; in vitro spntaneous differentiation and tumorigenesis in vivo would be strictly controlled. In conclusion, stem cell therapy is continously growing at a high rate, it truly becomes an essential treatment in modern medicine.

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Competing interests

The authors declare that they have no competing interests.

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