Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.51.008178

Clinical Application of Mesenchymal Stem Cells for Cancer Therapy: A Review of Registered Clinical Trials

Tuong Thi Van Thuy[1]*, Dao Van Toan[2] and Nguyen Duc Phuc[3]

[1]*Tuong Thi Van Thuy, Stem Cell Center, Phu San Ha Noi Hospital, Vietnam*

[2]*Dao Van Toan, Stem Cell Center, Phu San Ha Noi Hospital, Vietnam*

[3]*Nguyen Duc Phuc, Department of Oncology, Phu San Ha Noi Hospital, Vietnam*

***Corresponding author:** Tuong Thi Van Thuy, Tuong Thi Van Thuy, Stem Cell Center, Phu San Ha Noi Hospital, Ha Noi, Vietnam

ARTICLE INFO

Received: July 17, 2023

Published: August 01, 2023

Citation: Tuong Thi Van Thuy, Dao Van Toan and Nguyen Duc Phuc. Clinical Application of Mesenchymal Stem Cells for Cancer Therapy: A Review of Registered Clinical Trials. Biomed J Sci & Tech Res 51(5)-2023. BJSTR. MS.ID.008178.

ABSTRACT

Mesenchymal stem cells (MSCs) were discovered in the 1970s with their unique properties of differentiation, immunomodulation, multiple secreting, and homing factors to injured organs. MSC-based therapies have emerged as a promising strategy for various diseases such as cancer, tissue regeneration, or immunologic/inflammatory-related diseases. This study evaluated the clinical application of MSCs for cancer therapy in trials registered on ClinicalTrial.gov as of July 2022. The results showed 40 clinical trials used MSCs in various cancer conditions. 62% of trials used MSCs for therapeutic purposes to minimize the side effects of cancer treatment. Besides, 38% of trials were focused on using MSCs as a therapeutic agent to directly treat cancer. Most trials (38/40) are ongoing phase I/II, and 2 are entering phase III. 84% of trials used allogeneic MSCs compared with 13% using autologous sources, and 3% using both. 25/40 trials showed participants received a single dose of MSCs, while the most times were 12 times in a pancreatic cancer treatment trial. Conclusion: MSC-based therapy for cancer in clinical trials should be applied to [1] minimize the side effects of oncological treatments and [2] directly affect the tumor via selectively delivering anti-cancer payloads to tumor cells. Allogeneic MSCs are a priority selected in clinical cancer therapy.

Keywords: Mesenchymal Stem Cells; MSC-Based Therapy; Cancer Condition; Cancer Treatment; Clinical Trials

Introduction

Mesenchymal stem cells (MSCs) were discovered quite early in the 1970s (Friedenstein, Chailakhjan [3]). But many years later, the characteristics, differentiation, and potential of mesenchymal stem cells and clinical applications are focused on research and evaluation (Horwitz, et al. [4]). Due to their unique properties of differentiation, immune-regulatory ability, secretion of many growth factors, and inhibition and migration to damaged tissues, MSCs are currently one of the most widely studied topics in experimental medicine (Stefańska, et al. [5]). Similar to damaged tissue, tumor tissue also secretes chemotactic substances that attract MSCs to migrate to the tumor site. When infiltrating the tumor, MSCs interact with tumor cells and the surrounding healthy tissue environment to directly and indirectly affect tumor formation and growth directly and indirectly (Aravindhan, et al. [2,6]). Moreover, the collection of MSCs can be done easily, with minimally invasive procedures, and rapid mass expansion through laboratory culture. Thus, it is interesting about the use of MSCs therapy is maximized for precise and personalized medicine. Thanks to the evidence for the efficacy of MSCs cell therapy in cancer treatment in the laboratory (*in vitro*) (Akimoto, et al. [1,7-8]) and experimental animal models (*in vivo*) (Scioli, et al. [9]); there have been numerous registered clinical trials, which are being performed in the field of oncology over the current decades. Therefore, we conducted a meta-analysis of clinical trials using MSCs in the treatment of various cancer conditions, registered on ClinicalTrials.gov with the goal of:

1. Determining the purpose of using MSCs therapy in the clinical trials
2. Evaluating relevant factors of MSCs therapy such as characteristics of MSCs, and usage of MSCs in the clinical trials.

Material and Methods

Subjects

Clinical trials that were registered on ClinicalTrials.gov were reported to use MSCs in the treatment of cancer in various conditions. This is a database of clinical studies performed worldwide. The US National Library of Medicine provides this resource.

Method

Meta-analytical study. The defined search term is "cancer" in the Condition or Disease section and "mesenchymal stem cell" in the other terms as a therapeutic drug name. All clinical studies found that met the criteria for using MSCs in the treatment of cancer with various conditions as of July 2022 were included. Study data included clinical trial name, clinical trial number, country, the purpose of treatment, type of cancer, type of autologous/allogeneic MSCs, source of MSCs tissue, route of administration, therapeutic agent, the number of infusions, phase of the clinical trial, and sample size.

Results

Initial search results with defined terms showed 64 studies registered on ClinicalTrials.gov up to July 2022. But only 40 studies were identified to use MSCs in various cancer conditions. Details of the clinical trials are shown in (Supplementary Table 1). There are 38 clinical trials in phase I and phase II, and only 2 trials in phase III (Figure 1). The characteristics of MSCs in clinical trials are shown in (Table 1 & Figure 2). There is a variety of MSC sources, including bone marrow (11/40), adipose tissue (5/40), umbilical cord tissue (4/40), and cord blood (4/40). In addition, there was one registered trial that used cord tissue-derived MSCs for allogeneic transplantation and bone marrow-derived MSCs for autologous transplantation. However, in 16/40 trials, the authors did not disclose what type of MSCs used for therapy (Figure 2A). 84% of trials used allogeneic MSCs compared with 13% using autologous mesenchymal stem cell sources, and 3% using both sources (Figure 2B). For the MSCs-based therapeutic purpose of reducing the side effects of cancer treatments, a single dose was applied more 28 times than multiple doses (95% CI 2.8- 283.0) (Table 1).

Supplementary Table 1: Clinical trials using MSC therapy for cancer treatment.

Trial number	Country	Started year	Type of cancer	Purpose of therapy	Therapeutic agent	Dose Cells/ kg	Administration route
NCT02530047	USA	2015	Ovarian cancer	Tumor-targeted treatment	MSC-Interferon beta	$5x10^5$	Intraperitoneal
NCT01983709	USA	2013	Prostate cancer	Tumor-targeted treatment		$1x10^6$ $2x10^8$	Intervenous
NCT04087889	USA	2019	Pancreatics cancer	Tumor-targeted treatment		Unknown	Intervenous
NCT01844661	Spain	2013	Metastatic and Refractory Tumors	Tumor-targeted treatment	CELYVIR (MSC-ICOVIR5)	$2 x10^6$	Intervenous
NCT02068794	USA	2014	Recurrent ovarian, primary peritoneal, or fallopian tube cancer	Tumor-targeted treatment	MSC-MV-NIS (Oncolytic Measles Virus Encoding Thyroidal Sodium Iodide Symporter)	Unknown	Intraperitoneal
NCT02079324	Korea	2014	Head and Neck Cancer	Tumor-targeted treatment	GX-051 (Genetically Modified Mesenchymal Stem Cell)	Unknown	Intratumoral
NCT04657315	Korea	2020	Recurrent Glioblastoma	Tumor-targeted treatment	MSC11FCD the suicide gene, cytosine deaminase	$1x10^7$ $3x10^7$	Intratumoral
NCT03678467	USA	2018	Mandible Tumor	Tumor-targeted treatment	MSC-EB-CMF (MSC and biological materials)	Unknown	Implant
NCT03896568	USA	2019	Recurrent Glioblastoma/ Gliosarcoma/ Glioma	Tumor-targeted treatment	DNX-2401 (bone marrow-derived MSC)	Unknown	Intra-arterial
NCT05113342	USA	2021	Multiple Myeloma	Tumor-targeted treatment	Descartes-25 (allogeneic MSC)	Unknown	Intravenous
NCT05047276	Spain	2021	Uveal Melanoma in hepatic metastases	Tumor-targeted treatment	ALOCELYVIR (MSC-ICOVIR5)	Unknown	Intravenous
NCT03298763	UK	2017	Lung cancer	Tumor-targeted treatment	MSC-TRAIL	Unknown	Intravenous
NCT03696485	Israel	2019	Secondary Progressive Multiple Sclerosis	Tumor-targeted treatment	SCM-010 (adipose-derived MSC)	Unknown	Intrathecal
NCT01207193	Iran	2010	Bone cancer	Tumor-targeted treatment		Unknown	Bone defect

NCT04758533	Spain	2021	Recurrent Glioma	Tumor-targeted treatment	AloCELYVIR (MSC-ICO-VIR5)	5x105	Intravenous
NCT03106662	Turkey	2017	Hematological malignancies	graft-versus-host disease (GVHD)		$2x10^8$ $8x10^8$	Intravenous
NCT02648386	China	2016	Rectal cancer	Erectile Dysfunction		$5 x10^6$	
NCT01275612	Italy	2011	Solid tumor	Acute kidney failure in patient with cysplatin treatment		$1x10^6$ $2x10^6$ $5x10^6$	Intravenous
NCT00504803	Belgium	2007	Hematologic Neoplasms	graft-versus-host disease (GVHD)		Unknown	Intravenous
NCT00851162	USA	2009	Bone Neoplasms	Maxillary Cyst Bone Loss of Substance	Trinity MSC	Unknown	Intra-bone defect
NCT04776538	Denmark	2021	Head and Neck Cancer	Xerostomia Following Radiotherapy		Unknown	
NCT00361049	USA	2006	Hematological cancer	graft-versus-host disease (GVHD)		Unknown	
NCT02509156	USA	2015	Cancer with Anthracyclines treatment	anthracycline-induced cardiomyopathy (AIC)		$2 x10^6$	Unknown
NCT02804945	USA	2016	Cancerous Malignancies	acute respiratory distress syndrome (ARDS)		$3 x10^6$	Unknown
NCT02513238	Denmark	2015	Head and Neck Cancer	Xerostomia Following Radiotherapy		$1 x10^6$	Submandibularis
NCT04565665	USA	2020	Cancer with Covid-19	Acute respiratory distress syndrome (ARDS)			Intravenous
NCT01092026	Belgium	2010	Hematological Malignancies	Graft-versus-host disease (GVHD)			Intravenous
NCT01089387	France	2020	Prostate Cancer	Erectile Dysfunction			
NCT01389661	Spain	2011	Bone cancer	Maxillary Cyst Bone Loss of Substance	MSV-H (bone marrow-derived MSC)		Implant
NCT00081055	USA	2004	Hematological Malignancies	Hematological Malignancies	OTI-010 (autologous MSC)		
NCT02181478	USA	2014	Hematological Malignancies	Rejected graft		$2 x10^6$	Intraosseous
NCT00498316	USA	2007	Myelodysplastic Syndrome	Rejected graft		Unknown	Intravenous
			Leukemia				
NCT01045382	Belgium	2010	Myelodysplastic Syndromes	Rejected graft		$1.5x10^6$ $3x10^6$	Intravenous
NCT03184935	China	2017	Myelodysplastic Syndromes	Rejected graft		Unknown	Intravenous
NCT01129739	China	2010	Myelodysplastic Syndromes	Rejected graft		$1 x10^6$	Intravenous
NCT03066245	Jordan	2017	Bone cancer	Maxillary Cyst Bone Loss of Substance	MSC-PLGA (biological materials)	$1x10^6$	Intra-bone defect
NCT02962661	USA	2016	Hematological cancer	Anthracycline-induced cardiomyopathy (AIC)		Unknown	Intravenous
NCT03096782	USA	2015	Leukemia, Lymphoma	Rejected graft		Unknown	Intravenous
NCT01624701	Singapore	2012	Leukemia, Lymphoma	Rejected graft		Unknown	Intravenous
NCT00790413	Sweden	2008	Neuroblastoma	Rejected graft		Unknown	Intravenous

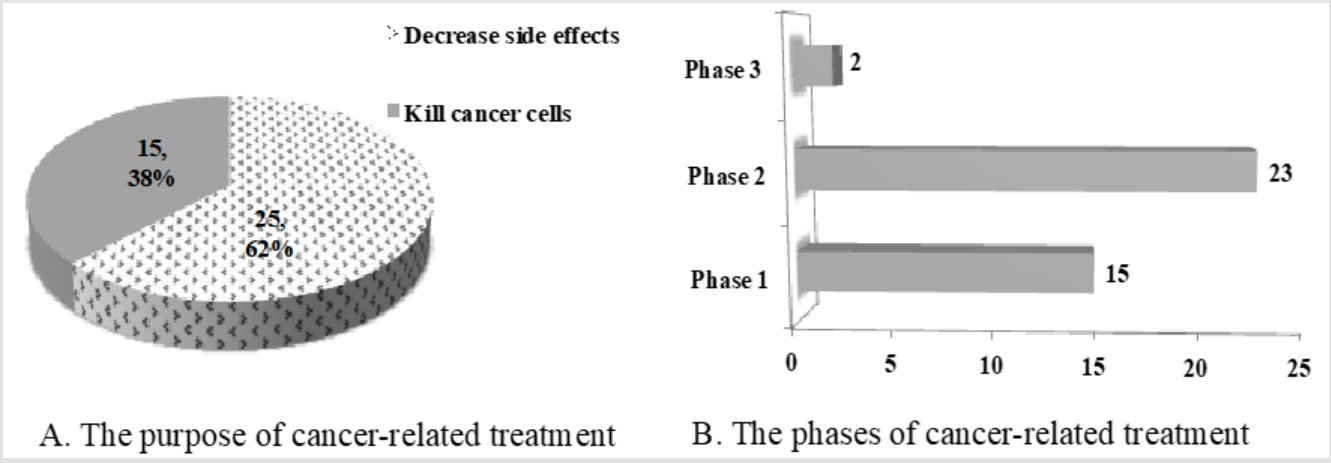

Figure 1: Clinical trials of MSCs in cancer treatment.
A. The purpose of cancer-related treatment.
B. The phase of cancer-related treatment.

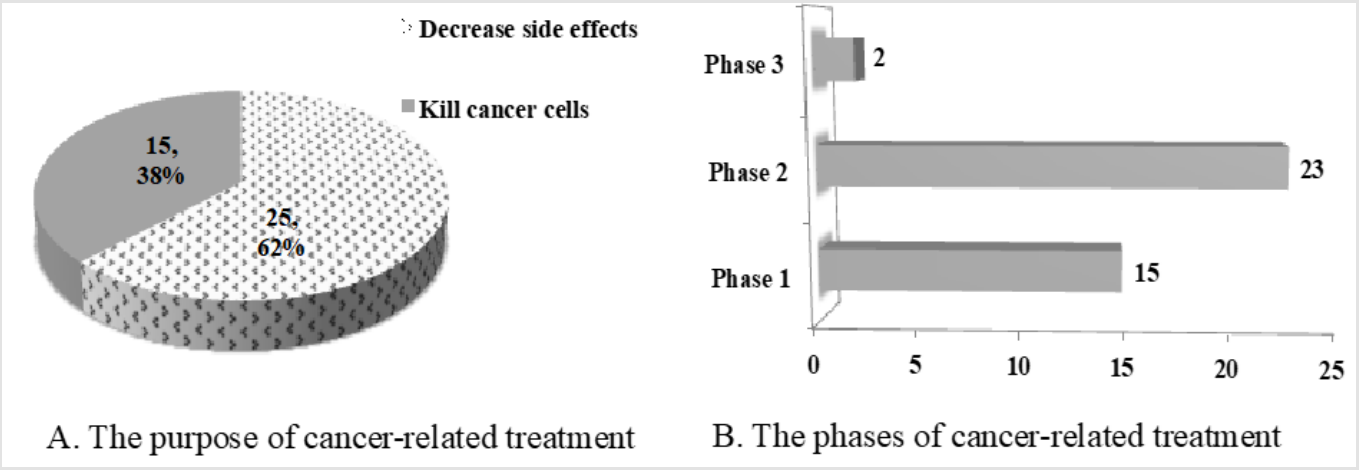

Figure 2: Sources of MSCs in cancer-related clinical trials.
A. Histological sources of MSCs. UC-MSC: umbilical cord-derived MSC, UB-MSC: umbilical blood-derived MSC, AD-MSC: adipose-derived MSC, BM-MSC: bone marrow-derived MSC.
B. Donor source of MSCs. Auto: Autologous MSC, Allo: Allogeneic MSC.

Table 1: Target of MSCs-based cancer therapy and relevant factors of MSCs therapy.

Target	Decrease complications	Direct tumor cells	OR (CI95%)
Times of MSC-based therapy			
One time	20	5	28 (2.8-283.0)
Multi-times	1	7	
Type of transplantation			
Autologous	4	1	2.7 (0.3-27.4)
Allogenic	19	13	

Discussion

The purpose of MSCs-Based Cancer Therapy in a Clinical Trial

The results showed that out of 40 trials, 25 evaluated the potential of MSCs to ameliorate the adverse events that occurred in conventional anticancer therapies, such as hemorrhagic cystitis due to radiation therapy (NCT02814864), xerostomia following radiotherapy (NCT03874572), anthracyclines-induced cardiomyopathy (NCT02509156), cisplatin-induced acute renal failure (NCT01275612), radiation-induced xerostomia (NCT03874572), erectile dysfunction after treatment for prostate

cancer (NCT01089387) or radiation-induced hemorrhagic cystitis (NCT02814864). In addition, 15 studies mentioned the possibility of using MSCs as "carriers" of therapeutic agents that directly act on killing cancer cells. The antineoplastic agents for transferring into MSCs may be the cytokines INFβ (NCT0253047), TNF-related apoptosis ligand (MSCTRAIL) (NCT03298763), or the oncolytic adenovirus ICOVIR5 (CELYVIR) (NCT05047276). Notably, in the NCT01844661 trial using CELYVIR to treat metastatic solid tumors or refractory tumors in children and adults, initial results have been published. Two adult patients with neuroblastoma showed a stable condition, and one of the patients continued treatment for another 6 weeks. The authors concluded that multiple doses of CELYVIR had good safety and beneficial anti-tumor effects (Ruano, et al. [10]). Interestingly, the authors noted that the disease condition in one pediatric patient after 3 years of treatment with CELYVIR was completely improved (García-Castro, et al. [11]). Thus, two clear goals of MSCS therapy in cancer treatment have been identified. There are to reduce the side effects of traditional cancer treatments and to directly affect the tumor cell through its ability of anti-cancer payloads to tumor cells.

The Characteristics of Clinical Trials Using MSCs-Based Therapy on Cancer

Most of these trials (38/40) are phase I and phase II, which are in the process of evaluating mainly the safety, appropriate dose, and initial effectiveness of MSC application on cancerous patients. In parallel, there were 2 trials (NCT03106662, NCT00851162) in phase III registered on ClinicalTrials.gov to help evaluate the clinical effectiveness of this new method on a broader scale. The predominant use of allogeneic MSCs in clinical trials compared with autologous MSCs. Furthermore, there was no association between the goals of MSCs therapy in cancer treatment and the autologous or allogenic transplantation of MSCs. This demonstrates the acceptance of scientists and clinicians about the ability to safely tolerate allogeneic MSCs as well as the convenience and ease of providing stem cell sources for this therapeutic activity. Diversification of MSCs sources, especially MSCs from tissue sources that are considered waste medical products such as adipose tissue, umbilical cord blood, and the umbilical cord is considered a new trend in modern medicine when banks of common stem cell banks are increasingly expanding the scope of sample source (Harris [12]). Regarding how to use MSCs, all trials mentioned the used dose, how many times infusions were, and the route to insert MSCs into the patients. The lowest dose of MSCs was 5 x 105 cells/kg (NCT02530047, NCT04758533) and the highest dose was 8 x 108 cells/kg (NCT03106662). 25/40 trials included a single dose of MSCs transplantation, while the most times of stem cell infusions were 12 times in a pancreatic cancer trial (NCT04087889). The authors tend to use low and repeated doses (doses below 106 cells/kg), and doses were repeated weekly. Besides, the authors often use high doses as a single dose. Interestingly, it can be observed that, with clinical trials using MSCs therapy for direct tumor treatment, MSCs are more likely to be selected for transplantation in more than 1 dose.

Meanwhile, for the purpose of preventing complications, MSCs therapy is usually applied in a single dose more than multi doses (OR=28, 95% CI: 2.8 – 293.0). Next, the route used to bring MSCs into the body includes 2 groups. The first administration route includes the ways to insert MSCs into the body through the vascular route; the most common was still the intravenous route. In addition, the intra-arterial route was also mentioned (NCT03896568). The second group is to deliver MSCs directly to the target tissue site such as direct injection into the tumor (NCT02079324, NCT04657315) or seeding MSCs into biological materials (scaffold) and then grafting into the patient's body at the tumor site where the tumor has been removed. On the other hand, depending on the cause, some other routes were also mentioned, such as intraperitoneal injection for ovarian cancer (NCT02530047). Although initial results are still in the follow-up phase, the potential of MSCs in cancer treatment has been recognized. The next challenge for scientists and clinicians is to explore the interactions between MSCs and cancer cells to eliminate or control cancer cells. Clinical trials need to be carried out at later phases so that application and effect would be evaluated comprehensively on an enormous area. It hopes that many publications on MSC-based therapy in the field of cancer treatment will be reported soon. Besides patients with cancer will approach an effective and safe therapeutic product that improves survival and quality of patient life.

Conclusion

The use of MSCs in cancer treatment is being tested as a combination treatment for 2 purposes: 1) participating in attenuating the systemic effects of traditional cancer treatments in patients, and 2) participating as a therapeutic agent to directly attack cancerous cells via its ability of anti-cancer payloads to the tumor location. in the synergistic enhancement of tumor-killing efficiency in cancer patients and undergoing and finishing cancer therapies. The trend of using allogeneic MSCs is dominant; this brings up the MSCs- provided convenience for treatment as well as the initially recognized safety of this type of stem cells.

Acknowledgment

This work is supported by the Vietnam Association of Japan Alumni (VAJA) and Toshiba International Foundation (TIFO).

References

1. Akimoto K, Kimura K, Nagano M, Takano S, To a Salazar G, et al. (2013) Umbilical cord blood-derived mesenchymal stem cells inhibit, but adipose tissue-derived mesenchymal stem cells promote glioblastoma multiforme proliferation. Stem Cells Dev 22(9): 1370-1386.
2. Aravindhan S, Ejam SS, Lafta MH, Markov A, Yumashev AV, et al. (2021) Mesenchymal stem cells and cancer therapy: insights into targeting the tumor vasculature. Cancer Cell Int 21(1): 158.
3. Friedenstein AJ, Chailakhjan RK, Lalykina KS (1970) The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Tissue Kinet 3(4): 393-403.
4. Horwitz EM, Le Blanc K, Dominici M, Mueller I, Slaper Cortenbach I, et al.

(2005) Clarification of the nomenclature for MSC: The International Society for Cellular Therapy position statement. Cytotherapy 7(5): 393-395.

5. Stefańska K, Bryl R, Moncrieff L, Pinto N, Shibli JA, et al. (2020) Mesenchymal stem cells – a historical overview %J Medical Journal of Cell Biology 8(2): 83-87.
6. Hmadcha A, Martin Montalvo A, Gauthier BR, Soria B, Capilla Gonzalez V (2020) Therapeutic Potential of Mesenchymal Stem Cells for Cancer Therapy. Front Bioeng Biotechnol 8: 43.
7. Lu L, Chen G, Yang J, Ma Z, Yang Y, et al. (2019) Bone marrow mesenchymal stem cells suppress growth and promote the apoptosis of glioma U251 cells through downregulation of the PI3K/AKT signaling pathway. Biomed Pharmacother 112: 108625.
8. Qiao L, Xu ZL, Zhao TJ, Ye LH, Zhang XD (2008) Dkk-1 secreted by mesenchymal stem cells inhibits growth of breast cancer cells via depression of Wnt signalling. Cancer Lett 269(1): 67-77.
9. Scioli MG, Artuso S, D Angelo C, Porru M, D Amico F, et al. (2018) Adipose-derived stem cell-mediated paclitaxel delivery inhibits breast cancer growth. PLoS One 13(9): e0203426.
10. Ruano D, López Martín JA, Moreno L, Lassaletta Á, Bautista F, et al. (2020) First-in-Human, First-in-Child Trial of Autologous MSCs Carrying the Oncolytic Virus Icovir-5 in Patients with Advanced Tumors. Mol Ther 28(4): 1033-1042.
11. García Castro J, Alemany R, Cascalló M, Martínez Quintanilla J, Arriero Mdel M, et al. (2010) Treatment of metastatic neuroblastoma with systemic oncolytic virotherapy delivered by autologous mesenchymal stem cells: an exploratory study. Cancer Gene Ther 17(7): 476-483.
12. Harris DT (2014) Stem Cell Banking for Regenerative and Personalized Medicine. Biomedicines 2(1): 50-79.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.51.008178

Tuong Thi Van Thuy. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php