

Analysis of the Expectation of Stem Cell Therapy in Patients with Alzheimer's Disease

Seokgil Han, Hojin Choi, Young Seo Kim, Kyu-Yong Lee, Young Joo Lee, Seong-Ho Koh

Department of Neurology, Hanyang University College of Medicine, Seoul, Korea

Background and Purpose Alzheimer's disease (AD) is the most common form of dementia which typically manifests as loss of memory and cognitive functions. Currently, available treatments for AD provide only symptomatic improvement and the benefit is minimal. Stem cell therapy (SCT) has been considered a promising treatment option for AD. We investigated the caregiver's perception about implementation of SCT in their AD patients, and determined the factors related to SCT.

Methods A total of 100 caregivers, who cared for their AD patients, were interviewed at two hospitals. Structured open and closed questions about SCT for AD were asked by trained interviewers using the conventional in-person method. In addition, 60 dementia-related physicians were randomly interviewed via an e-mail questionnaire.

Results Of the 100 subjects, 61 caregivers replied that they wanted their AD patients to receive SCT. Approximately 50% of the caregivers expected high improvement in cognitive function, behavioral and psychological symptoms, and activities of daily living, and physical improvements among their AD patients. However, physicians had much lower expectations of improvements in the above parameters. Multivariate analysis revealed that female gender [odds ratio (OR): 3.747, 95% confidence interval (CI): 1.425–9.851] and familiarity with stem cells (OR: 3.873, 95% CI: 1.290–11.622) were independently associated with caregivers' desire that their AD patients should undergo SCT. The major source of information on SCT was television (76.7%), and the most reliable source of information on SCT was physicians (83.6%).

Conclusions In this study, many caregivers of AD patients fantasized and overestimated the need for SCT in comparison with physicians' expectation. Therefore, it is necessary for physicians to develop strategies for educating caregivers about the appropriate risks and benefits of SCT.

Key Words Alzheimer's disease, caregiver, stem cell therapy.

Received: November 3, 2016 **Revised:** November 22, 2016 **Accepted:** November 22, 2016

Correspondence: Seong-Ho Koh, MD, PhD, Department of Neurology, Hanyang University College of Medicine, Guri Hospital, 153 Gyeongchun-ro, Guri 11923, Korea

Tel: +82-31-560-2267, **Fax:** +82-31-560-2267, **E-mail:** ksh213@hanyang.ac.kr

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, and the prevalence of AD in a population usually increases with age. After the age of 65, the risk of developing AD doubles every 5 years, so that by the age of 85, some researchers suggest that about half of the individuals will have this disease. Several estimates have predicted that there could be more 125 million patients with AD in the world by 2050.¹

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Therefore, many studies have tried to discover a therapeutic approach for AD.² Currently, the only approved therapeutics for AD are acetylcholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist which provide transient symptomatic improvement or minimal benefit in terms of modifying the overall course of the disease.³⁻⁵

Stem cell therapy (SCT) may be one of the promising treatment options that may improve the patient's outcome in AD. SCT may have beneficial effects, such as replacing the neurons,^{6,7} protecting them,⁸ preventing inflammation,⁹ and promoting angiogenesis.¹⁰ Based on these expectations, there are many ongoing controlled trials of SCT for a lot of diseases, especially neurodegenerative diseases. However, preclinical and

clinical evidence to support its efficacy in AD is still not available. For many neurodegenerative disorders such as Parkinson's disease, stem cell-based therapies aim to replace specific structures or neurotransmitters. Unfortunately in AD, because there are a lot of related neuronal systems and neurotransmitters, cell replacement strategies are considered a challenging approach. Since there is currently no proven SCT for AD, reckless trials of SCT may be accompanied by physical and financial risks. For example, there have been reports of brain tumors and death after SCT.^{7,8} Despite several serious risks, many caregivers who are not satisfied with the current treatments for their AD patients are willing to try SCT.⁹

The importance of appropriate governance of advanced science has been discussed,¹⁰ but inappropriate SCTs are still being used in many countries, and the number of patients receiving SCT is greatly increasing.¹¹ Therefore, caregivers need to have a better understanding of SCT to avoid inappropriate treatments for their AD patients. This baseline understanding may be essential for establishing correct treatment strategies. Several surveys have been performed to assess the publics' understanding of stem cell research.^{12,13} However, to the best of our knowledge, there are no studies evaluating caregivers' knowledge about SCT, except for our previous report in stroke patients.¹⁴ We aimed to investigate the baseline knowledge of caregivers on SCT, to confirm the factors related to caregivers who would like their AD patients to receive SCT, and to compare the results with those of our previous report in stroke patients.¹⁴

METHODS

This study was designed as a prospective, multicenter, consecutive study conducted at 2 hospitals in Seoul and Guri, Korea. We used a similar protocol to compare the similarities and differences in the results between this study and the previous study¹⁶ which we had performed in chronic ischemic stroke patients. Caregivers of patients who had been diagnosed with AD by neurologists or psychiatrists at least 3 months previously were included. Patients with AD met the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria for probable AD. Exclusion criterion was diagnosis of disease with another type of dementia.

Caregivers who were not able to communicate were excluded. There were no public campaigns or educational efforts before or during this study. This study was approved by the Institutional Review Board of Hanyang University Guri hospital. The study was performed from January 2013 to June 2013 and recruitment was stopped when the total number of

patients reached 100. All consecutive caregivers of patients with AD in the outpatient departments of the 2 hospitals were reviewed to confirm their eligibility. After obtaining current neurological scales, such as Korean version of Mini-Mental State Examination (K-MMSE)¹⁵ and Clinical Dementia Rating (CDR),¹⁶ physicians, who had been formally trained in the use of standardized definitions and data collection techniques, conducted in-person interviews with all eligible caregivers. The caregivers were interviewed within 5 minutes after providing verbal informed consent. Caregivers who did not consent to participate in the study were excluded. The interviews were conducted in Korean and there was no attempt to prompt the respondents. The survey instrument contained 4 sections. In the first section, the questions were about demographic characteristics, including age, sex, education level, housing status, and the presence of risk factors (smoking, alcohol, hypertension, diabetes mellitus, hyperlipidemia, heart disease, head trauma history, stroke history and family history). In the second section, information about AD, such as onset, disease duration and clinical symptoms was obtained. In the third section, caregivers were asked closed questions about whether they wanted their AD patients to receive SCT in spite of its unknown side effects. We also asked questions about knowledge, attitudes, and expectations of SCT, and regarding what was thought to be a reasonable price. Finally, in the fourth section, caregivers were asked, using closed-ended multiple-choice questions, to name all sources from which they had obtained SCT-related information. Those who wanted their AD patients to receive SCT were asked, using closed-ended single choice questions, to name their most reliable source of information. In addition to the caregiver survey, we also performed a physician survey among those who may encounter patients with AD, to determine if the lack of knowledge on the part of the patients was due to lack of communication with their physicians. We sent 250 e-mails to randomly sampled neurologists and psychiatrists and analyzed the first 60 completed questionnaire forms. The survey instruments included the following factors: age, sex, specialization, knowledge, perspective, expectation, reasonable price and whether they would recommend SCTs.

Statistical analysis

Baseline characteristics of caregivers of AD patients were recorded as means (standard deviation) and numbers (percentages). The patients were divided into 2 groups according to whether their caregivers wanted them to receive SCT or not. We compared the explanatory variables by the chi-square test, the Student's *t*-test, or the Mann-Whitney U test, wherever appropriate. Using a multivariable logistic regression

analysis, we investigated the independent effects of demographics, the presence of risk factors, and outcome scale scores for the patients whose caregivers wanted them to undergo SCT. Interactions between variables were also assessed. Explanatory variables identified by the univariate analysis at $p < 0.2$ were used in the model. All significance tests were 2-tailed, and differences were considered statistically significant at $p < 0.05$. Data were analyzed with SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 100 patients registered in the present study who were cared by caregivers, 60 patients (60%) were female and 40 patients (40%) were male. The mean age was 76.7 years and the age range was 63–93 years. The demographic characteristics of the AD patients are shown in Table 1. The mean score of the K-MMSE was 17.9 and the number of patients assessed as CDR 1 and 2 was 75 and 25, respectively. Among the caregivers, 43 caregivers (43%) replied that they had heard about stem cells, and 17 caregivers (17%) stated that they knew about the ongoing worldwide clinical trials of SCT for AD patients. Sixty-one caregivers (61%) replied that they wanted their AD patients to receive SCT in spite of the unknown side effects. Of the 61 caregivers who replied that they would like their AD patients to receive SCT, the largest proportion of caregivers (52.5%) replied that less than \$1000 was a reasonable price, followed by \$1000–\$5000 (34.4%). Only 9 caregivers would have liked their AD patients to receive SCT at a cost of \$5000–\$10000, and 5 caregivers replied that they would like their AD patients to receive SCT even at a cost exceeding \$10000 (Table 2). When caregivers answered the questions about what they expected from SCT for their AD patients, improvement in cognitive function, behavioral and psychological symptoms, activities of daily living and physical improvements were highly expected by 34 (55.7%), 30 (49.2%), 28 (45.9%), and 28 (45.9%) responders, respectively (Fig. 1).

The clinical characteristics of the patients in the 2 subgroups are also shown in Table 1. Sex of the patients (female gender), disease duration, hyperlipidemia and familiarity with stem cells were significantly associated with a desire for undergoing SCT in univariate analysis. In multivariable logistic regression analysis, female gender [odds ratio (OR): 3.747, 95% confidence interval (CI): 1.425–9.851, $p = 0.007$] and familiarity with stem cells (OR: 3.873, 95% CI: 1.290–11.622, $p = 0.016$) were independent factors associated with caregivers' desire that their AD patients should undergo SCT (Table 3). The most common sources of information are listed in Table 4. Television (76.7%) was the most frequently cited source of informa-

Table 1. Clinical characteristics of AD patients whose caregivers wanted them to undergo stem cell therapy versus clinical characteristics of AD patients whose caregivers did not want them to undergo stem cell therapy

	Want stem cell therapy		<i>p</i>
	Yes	No	
Demographics			
Age (years)	76.4	77.1	0.572*
Gender (female)	57.5	26.7	0.002
Education (years)	4.4	5.6	0.235
Disease duration			
Months	30.4	45.5	0.041†
Risk factors (%)			
HTN	50.8	59	0.425
DM	42.6	38.5	0.68
Hyperlipidemia	42.6	17.9	0.01
Head trauma	14.8	17.9	0.671
Family history	14.8	25.6	0.176
K-MMSE			
Scores	18.5	17.1	0.238†
CDR, scores (%)			
1	75.4	74.4	0.906
2	24.6	25.6	
Familiarity with stem cells (%)	54.1	25.6	0.005
Knowledge of stem cells			
clinical trials for dementia (%)	18	15.4	0.731

Pearson's χ^2 test was used.

*Student's *t*-test, †Mann–Whitney U test were used.

“Familiarity with stem cells” indicates the patients who answered that they had heard about stem cells. “Knowledge of stem cells clinical trials for dementia” indicates the patients who answered that they knew about stem cell clinical trials for stroke.

CDR: Clinical Dementia Rating, DM: diabetes mellitus, HTN: hypertension, K-MMSE: the Korean Mini-Mental State Examination.

Table 2. Caregivers' and physicians' views about stem cell therapy for AD patients

	Caregivers	Physicians	<i>p</i>
	(<i>n</i> =100)	(<i>n</i> =60)	
Familiarity with stem cells (%)	43	100	<0.001
Knowledge of stem cells			
clinical trials for dementia (%)	17	55	<0.001
Want stem cell treatment (%)	61		
Would recommend stem cell treatment		48.3	
Reasonable price, \$ (%)*			
1000<	52	13.3	<0.001
1000–5000	34	18.3	
5000–10000	9	51.7	
>10000	5	16.7	

Pearson's χ^2 test was used.

*Answers concerning a reasonable price were obtained from caregivers and physicians.

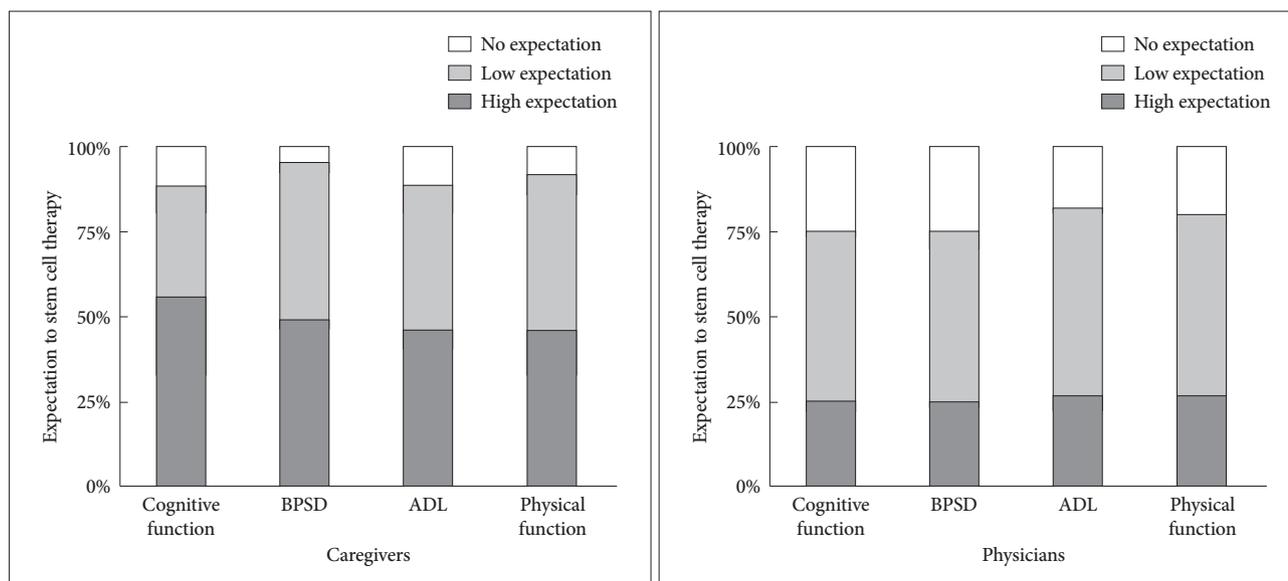


Fig. 1. Expectations concerning stem cell therapy among caregivers and physicians. Almost half of the respondents thought that it would be highly effective. However, physicians had relatively low expectations from the use of stem cell therapies. ADL: activities of daily living, BPSD: behavioral and psychological symptoms of dementia.

Table 3. Multivariable logistic regression analysis: factors associated with stem cell therapy

	Caregivers who wanted stem cell therapy for AD patients		
	Crude OR (95% CI)	Adjusted OR (95% CI)	<i>p</i> *
Gender, female	3.721 (1.592–8.694)	3.747 (1.425–9.851)	0.007
Familiarity with stem cells	3.418 (1.421–8.221)	3.873 (1.290–11.622)	0.016

Candidate variables were those from the univariate analysis with *p*<0.2.

**p* for multivariable model.

AD: Alzheimer’s disease, CI: confidence interval, OR: odds ratio.

Table 4. Sources of information about stem cell therapies

	Source of information (<i>n</i> =43)	Most reliable source (<i>n</i> =43)
Television	33 (76.7%)	5 (11.5%)
Internet	5 (11.6%)	2 (4.7%)
Physician	3 (7.0%)	36 (83.6%)
Friends/colleagues	2 (4.7%)	0 (0%)

tion, followed by the internet (11.6%) and physician (7.0%). However, doctors were considered the most reliable source of information (83.6%), followed by television (11.5%) and the internet (4.7%). After sending 250 e-mails, 78 (31.2%) physicians responded to the survey and the first 60 questionnaires were analyzed. Among them, 43 physicians (71.7%) were male and the mean age was 38.6 years with a range from 27 to 53 years. The respondents included 40 neurologists and 20 psychiatrists. All of the physicians had heard of stem cells, and 55 (91.7%) knew about the clinical trials being performed around the world. To compare with the caregivers’ survey, in which 61% indicated that they wanted their AD patients to receive SCT in spite of the unknown side effects,

only 29 physicians (48.3%) responded that they would recommend SCT and the reasonable price was much higher than that expected by the patients. The largest proportion of physicians (51.7%) answered that \$5000–\$10000 was a reasonable price, followed by \$1000–\$5000 (18.3%), and more than \$10000 (16.7%) (Table 2). Expectations of SCT in physicians were also different from those in caregivers. The majority of physicians had low expectations of improvements in cognitive function (50%), behavioral and psychological symptoms (50%), and activities of daily living (55%), and physical improvements (53.3%), respectively (Fig. 1).

DISCUSSION

In the previous study, we evaluated the attitudes or expectations of SCT in chronic ischemic stroke patients.¹⁶ Therefore, we could analyze the results of this study with reference to those of the previous study and could find some similarity or difference between the two studies.

First, 61% of caregivers of AD patients replied that they wanted their AD patients to receive SCT, and this proportion is

higher than that of patients with stroke (61% vs. 47%). They also had unrealistic expectations that SCT would improve cognitive function, behavioral and psychological symptoms, and activities of daily living and cause physical improvements in AD patients. Considering that unsafe SCTs are increasing rapidly and are widely attracting the patients,¹¹ caregivers do not have detailed information and patients can easily be exposed to unsafe SCTs. In the previous study, we reported that male gender and long disease duration in chronic stroke patients were independently associated with a desire for undergoing SCT, and these findings reflect patients' desire to regain social activity and recover from disability, because males may participate more in social activities than females, and patients with long disease duration may have more pronounced disabilities. However, in this study, female gender and familiarity with stem cells were independently associated with caregivers' desire that their AD patients should undergo SCTs. Therefore, we had to find other explanations for the results.

Most AD patients are in their seventies and are generally older than stroke patients. Therefore, caregivers of AD patients expect less social activities than those of stroke patients. Otherwise, most caregivers of AD patients consider more about family bonding and good activities of daily living. In this study, we noted that caregivers of female AD patients are more likely to want their patients to receive SCT because they might be contribute more to family life rather than social activities. Manifestations and symptoms of AD progress continuously and result in mental deterioration. It is a possible explanation that some caregivers may lose hope and are not ready for treatment of their AD patients as time passes. Therefore, it is a possible explanation that disease duration can have an inverse correlation with anticipation of receiving SCT.

Second, our study showed that caregivers expected too much from SCT. Although SCT for AD lagged far behind that for many other neurodegenerative disorders because of the widespread nature of AD pathology¹⁷ and current evidence for SCT in AD is less than that for SCT in stroke.¹⁷⁻²⁰ Almost 50% of our subjects expected high improvement in cognitive function, behavioral and psychological symptoms, and activities of daily living, and physical improvements. These findings suggest that caregivers do not have accurate knowledge of SCT in spite of their familiarity with stem cells from advertisements on television and internet. In contrast to caregivers' expectations, more than half of the physicians had low expectations of any improvements with SCT in AD. This disagreement in opinion may be due to deficient communication between caregivers and physicians during their visit to the clinics. Recently, a doctor's responsibility to inform the patients about the benefits and risks of SCT has been empha-

sized.^{21,22} In addition, our study also showed that television was the most frequently reported source of information on SCT and caregivers thought that physicians were the most reliable source of information on SCT. Therefore, we suggest that dementia specialists and physicians should make a greater effort to provide their patients and caregivers with detailed knowledge via television and internet media.

The final finding of interest concerns caregivers' thoughts about the cost of SCT. The actual cost has been reported to vary between US \$5000 and \$39500²⁴ and more than half of the physicians in our survey also indicated that the cost of SCT can be in the range of \$5000-\$10000. However, the majority (52%) of the caregivers thought that the reasonable price of SCT would be below \$1000. The difference between caregivers' ideas regarding the cost of SCT and the real price was similar to that in our previous study, and it may suggest that patients had not been directly exposed to commercial advertisements and they only had baseless hopes about SCTs.

There are some limitations to this study. The number of enrolled caregivers of patients might be too small to represent all caregivers. We were willing to evaluate patients' and caregivers' information in detail. Therefore, the sample size was restricted to 100, but in terms of the results, it might be too small. However, since we evaluated the same subjects who had chronic ischemic stroke in our previous study, we could compare the data between chronic ischemic stroke and AD. Therefore, we believe that our results provide valuable information about caregivers' understanding and expectation of SCT. An extension of the survey to other diseases and comparative studies would be of interest and they should be undertaken. Second, we could not investigate the patients' economic status and caregivers' educational status, which might be associated with the results. We included economic status and educational status in our survey list, but majority of caregivers were not willing to provide this information. Since insufficient data on economic status and educational status could lead to confusing results, we decided not to use this information in the present results. Third, we focused on mild to moderate AD patients because it would be difficult for severe AD patients and their caregivers to visit the hospital. Due to this reason, severe AD patients could have been ignored. We think that caregivers of severe AD patients might show similar results, but it should be investigated in further evaluation. Finally, we could not evaluate the difference between neurologists and psychiatrists or other physicians because initially, we did not consider the differences between these groups. Future study that compares the difference between neurologists and other physicians will be interesting.

Taken together, this study indicates that many caregivers fantasize about their AD patients receiving SCT and AD pa-

tients could be exposed to a substantial risk of inappropriate SCT if they do not receive proper information. This tendency was greater in AD compared with chronic ischemic stroke. Accurate strategies to educate patients and caregivers about the risks and benefits of SCT are needed to reduce the number of unproven stem cell therapies.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgements

This work was supported by a grant from the Korea Research Foundation (2015R1A2A2A04004865).

REFERENCES

1. Wimo A, Winblad B, Jönsson L. The worldwide societal costs of dementia: estimates for 2009. *Alzheimers Dement* 2010;6:98-103.
2. Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: clinical trials and drug development. *Lancet Neurol* 2010;9:702-716.
3. Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *Clin Interv Aging* 2008;3:211-225.
4. Roberson ED, Mucke L. 100 years and counting: prospects for defeating Alzheimer's disease. *Science* 2006;314:781-784.
5. Maggini M, Vanacore N, Raschetti R. Cholinesterase inhibitors: drugs looking for a disease? *PLoS Med* 2006;3:e140.
6. Lindvall O, Hyun I. Medical innovation versus stem cell tourism. *Science* 2009;324:1664-1665.
7. Amariglio N, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthal R, Trakhtenbrot L, et al. Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. *PLoS Med* 2009;6:e1000029.
8. Pontes-Neto OM, Silva GS, Feitosa MR, de Figueiredo NL, Fiorot JA Jr, Rocha TN, et al. Stroke awareness in Brazil: alarming results in a community-based study. *Stroke* 2008;39:292-296.
9. Enserink M. Biomedicine. Selling the stem cell dream. *Science* 2006;313:160-163.
10. Gaskell G, Einsiedel E, Hallman W, Priest SH, Jackson J, Olsthoorn J. Communication. Social values and the governance of science. *Science* 2005;310:1908-1909.
11. Ryan KA, Sanders AN, Wang DD, Levine AD. Tracking the rise of stem cell tourism. *Regen Med* 2010;5:27-33.
12. Shineha R, Kawakami M, Kawakami K, Nagata M, Tada T, Kato K. Familiarity and prudence of the Japanese public with research into induced pluripotent stem cells, and their desire for its proper regulation. *Stem Cell Rev* 2010;6:1-7.
13. Einsiedel E, Premji S, Geransar R, Orton NC, Thavaratnam T, Bennett LK. Diversity in public views toward stem cell sources and policies. *Stem Cell Rev* 2009;5:102-107.
14. Kim YS, Chung DI, Choi H, Baek W, Kim HY, Heo SH, et al. Fantasies about stem cell therapy in chronic ischemic stroke patients. *Stem Cells Dev* 2013;22:31-36.
15. Kang Y, Na DL, Hahn S. A validity study on the Korean Mini-Mental State Examination (K-MMSE) in dementia patients. *J Korean Neurol Assoc* 1997;15:300-308.
16. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993;43:2412-2414.
17. Chen WW, Blurton-Jones M. Concise review: can stem cells be used to treat or model Alzheimer's disease? *Stem Cells* 2012;30:2612-2618.
18. Dantuma E, Merchant S, Sugaya K. Stem cells for the treatment of neurodegenerative diseases. *Stem Cell Res Ther* 2010;1:37.
19. Lee JS, Hong JM, Moon GJ, Lee PH, Ahn YH, Bang OY. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. *Stem Cells* 2010;28:1099-1106.
20. Honmou O, Houkin K, Matsunaga T, Niitsu Y, Ishiai S, Onodera R, et al. Intravenous administration of auto serum-expanded autologous mesenchymal stem cells in stroke. *Brain* 2011;134(Pt 6):1790-1807.
21. Zarzeczny A, Caulfield T. Stem cell tourism and doctors' duties to minors—a view from Canada. *Am J Bioeth* 2010;10:3-15.
22. Regenber AC, Hutchinson LA, Schanker B, Mathews DJ. Medicine on the fringe: stem cell-based interventions in advance of evidence. *Stem Cells* 2009;27:2312-2319.